07/925,220

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 5,284,858

Docket No: Q29894 (ID004406)

Issued: February 8, 1994

Assignee: Sucampo AG

For: PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

MAIL STOP: Patent Term Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Sucampo AG ("Sucampo" or "the Applicant"), a corporation organized and existing under the laws of Switzerland, represents that it is the assignee of the entire interest in and to United States Letters Patent No. 5,284,858, granted to Ryuzo Ueno, Ryuji Ueno, Ichie Kato and Tomio Oda on February 8, 1994, for PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME by virtue of an Assignment from the inventors in favor of Kabushiki Kaisha Ueno Seiyaku Oyo Kenkyujo, recorded in the U.S. Patent and Trademark Office on October 18, 1989, at Reel 5167, Frame 423-424, and subsequently, an Assignment from Kabushiki Kaisha Ueno Seiyaku Oyo Kenkyujo to Sucampo AG, recorded in the U.S. Patent and Trademark Office on June 13, 2001, at Reel 011887, Frame 0481. A copy of each Assignment is attached hereto as Exhibit 1.

The Applicant, acting through its duly authorized attorney whose power to act on behalf of the Applicant is filed concurrently herewith, hereby submits this application for extension of

patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740).

For convenience, the information contained in this application will be presented in a format and order following the requirements of 37 C.F.R. § 1.740.

The Applicant for patent term extension, Sucampo AG, was not the marketing applicant before the regulatory agency; however, there was an agency relationship between the patent owner and the marketing applicant during the regulatory review period. To show that the Applicant is authorized to rely upon the activities of the marketing applicant before the Food and Drug Administration ("FDA"), the Applicant has obtained a letter specifically authorizing such reliance and attaches it hereto as Exhibit 2.

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE, OR CHARACTERISTICS

AMITIZA™, a soft gelatin capsule for oral administration, contains as the only active ingredient **lubiprostone**. The chemical name for lubiprostone is **(-)-7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid**, having the following structural formula:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 5,284,858

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Issued: February 8, 1994

Assignee: Sucampo AG

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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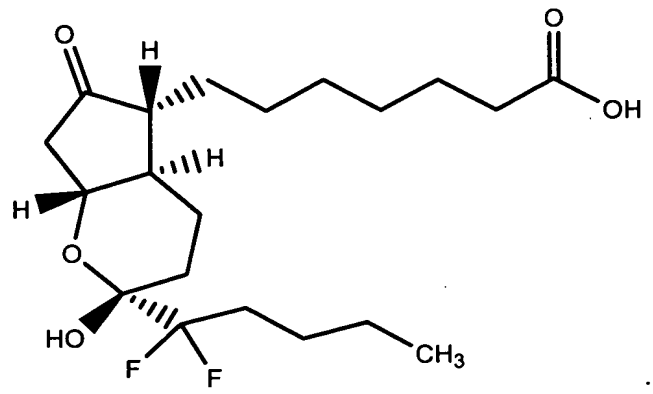


(2) **A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED.**

The approved product, AMITIZA™, was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505 (21 U.S.C. § 355).

(3) **AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED.**

The approved product, AMITIZA™, received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on January 31, 2006. A copy of the permission letter including Package Insert is attached hereto as Exhibit 3.

(4) **IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FDC ACT, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN**

ACT, OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED.

The active ingredient in AMITIZA™ is lubiprostone. Lubiprostone has not been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxic Act prior to the approval of NDA 21-908 by the Food and Drug Administration on January 31, 2006.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO 37 C.F.R. § 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED.

This application for Extension of Patent Term Under 35 U.S.C. § 156 is being submitted within the permitted sixty day period pursuant to 37 C.F.R. § 1.720(f). Said period will expire on April 1, 2006.

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION.

The complete identification of the Patent for which extension is being sought is as follows:

Inventors: Ryuzo Ueno, Ryuji Ueno, Ichie Kato, and Tomio Oda

U.S. Patent No.: 5,284,858

Issue Date: February 8, 1994

Expiration Date: February 8, 2011 (17 years after the issue date)

(7) **A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS.**

A complete copy of U.S. Patent No. 5,284,858 is attached hereto as Exhibit 4.

(8) **A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR REEXAMINATION CERTIFICATE ISSUED IN THE PATENT.**

No Disclaimer or Reexamination Certificate has been issued with respect to U.S. Patent No. 5,284,858.

A Certificate of Correction was requested and issued on September 7, 2004 with respect to U.S. Patent No. 5,284,858. A copy of the Certificate of Correction is attached hereto as Exhibit 5.

Maintenance fee payments have also been made for U.S. Patent No. 5,284,858; attached hereto as Exhibit 6 are papers relating to the maintenance fee payments, as follows:

(a) A Maintenance Fee Statement showing the status of the first maintenance fee payment required at 3 ½ years as "paid,"

(b) A Maintenance Fee Statement showing the status of the first maintenance fee payment required at 7 ½ years as "paid," and

(c) A Maintenance Fee Statement showing the status of the first maintenance fee payment required at 11 ½ years as "paid."

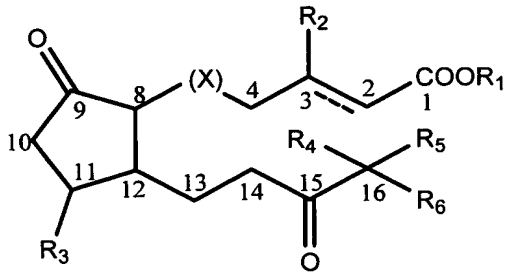
(9) **A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT**

CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE APPROVED PRODUCT.

U.S. Patent No. 5,284,858 claims the approved product, and also claims an anti-ulcer composition comprising the approved product and a method of using the approved product.

Claim 1

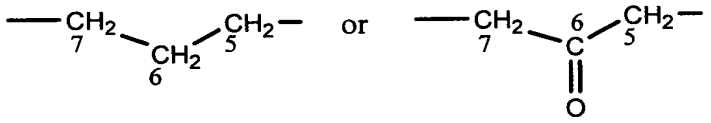
Prostaglandins E represented by a general formula:



(I)

in which

X represents:



R_1 represents: a hydrogen atom, a physiologically acceptable sat[1] residue, or an ester residue selected from the group consisting of alkyl, benzyl, hydroxyalkyl, alkoxyalkyl, alkylsilyl and tetrahydropyranyl group;

R_2 represents: a hydrogen atom or a methyl group;

R_3 represents: a hydroxyl or hydroxymethyl group;

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1 There is a typographical error in which "sat" should be "salt."

R_4 and R_5 each represents: a hydrogen atom, a methyl group or a halogen atom provided that at least one of R_4 and R_5 is a halogen atom; and

R_6 represents: a C_1-C_9 alkyl group which may have a branch or a double bond, or a C_1-C_9 alkyl group having an alkoxy substituent group, the C_2-C_3 bond being a single or double bond.

Claim 2

Prostaglandins E as described in claim 1, wherein R_4 and R_5 are halogen atoms.

Claim 3

Prostaglandins E as described in claim 1, wherein R_4 and/or R_5 is a fluorine atom.

Claim 4

Prostaglandins E as described in claim 1, wherein R_4 or R_5 is a methyl group.

Claim 5

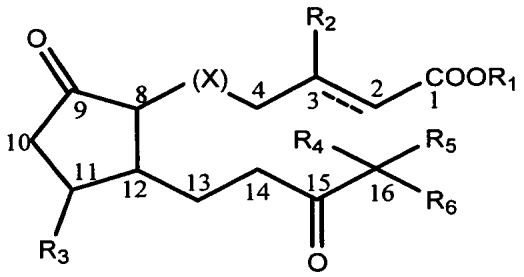
Prostaglandins E as described in claim 1, which is 13,14-dihydro-15-keto-PGE having one or more fluorine atom(s) on 16-position or alkyl ester thereof.

Claim 6

Prostaglandins E as described in claim 1, being 13,14-dihydro-6,15-diketo-16R,S-fluoro-PGE_1 or alkyl ester thereof.

Claim 7

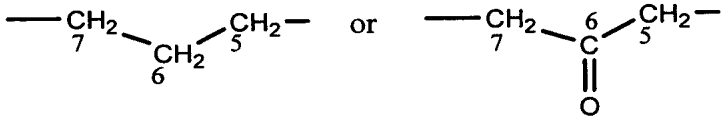
An anti-ulcer composition comprising an anti-ulcer effective amount of a prostaglandin E expressed by a general formula:



(I)

in which

X represents:



R_1 represents: a hydrogen atom, a physiologically acceptable sat[2] residue, or an ester residue selected from the group consisting of alkyl, benzyl, hydroxyalkyl, alkoxyalkyl, alkylsilyl and tetrahydropyranyl group;

R_2 represents: a hydrogen atom or a methyl group;

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[2] There is a typographical error in which "sat" should be "salt."

R_3 represents: a hydroxyl or hydroxymethyl group;

R_4 and R_5 each represents: a hydrogen atom, a methyl group or a halogen atom provided that at least one of R_4 and R_5 is a halogen atom; and

R_6 represents: a C_1-C_9 alkyl group which may have a branch or a double bond, or a C_1-C_9 alkyl group having an alkoxy substituent group, the C_2-C_3 bond being a single or double bond.

Claim 8

An anti-ulcer composition as in claim 7, wherein R_4 and R_5 are halogen atoms.

Claim 9

An anti-ulcer composition as in claim 7, wherein R_4 and/or R_5 is a fluorine atom.

Claim 10

An anti-ulcer composition as in claim 7, wherein R_4 or R_5 is a methyl group.

Claim 11

An anti-ulcer composition as in claim 7, wherein the prostaglandin E is 13,14-dihydro-15-PGE[3] having one or more fluorine atom(s) on 16-position or alkyl ester thereof.

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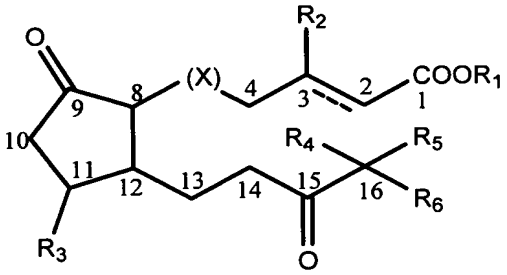
[3] "13,14-dihydro-15-PGE" should be "13,14-dihydro-15-keto-PGE." This is an obvious error in view of the formula (I) of claim 7, from which claim 11 depends.

Claim 12

An anti-ulcer composition as in claim 7, wherein the prostaglandin E is 13,14-dihydro-6,15-diketo-16R,S-fluoro-PGE_1 or alkyl ester thereof.

Claim 13

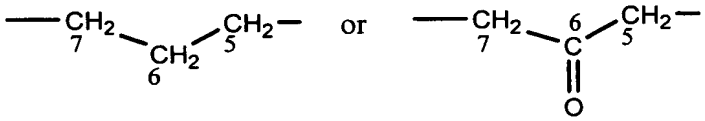
A treatment of ulcer by administering an anti-ulcer treating effective amount of prostaglandin E to a patient, wherein the prostaglandin E is represented by a formula:



(I)

in which

X represents:



R_1 represents: a hydrogen atom, a physiologically acceptable salt residue, or an ester residue selected from the group consisting of alkyl, benzyl, hydroxyalkyl, alkoxyalkyl, alkylsilyl and tetrahydropyranyl group;

R_2 represents: a hydrogen atom or a methyl group;

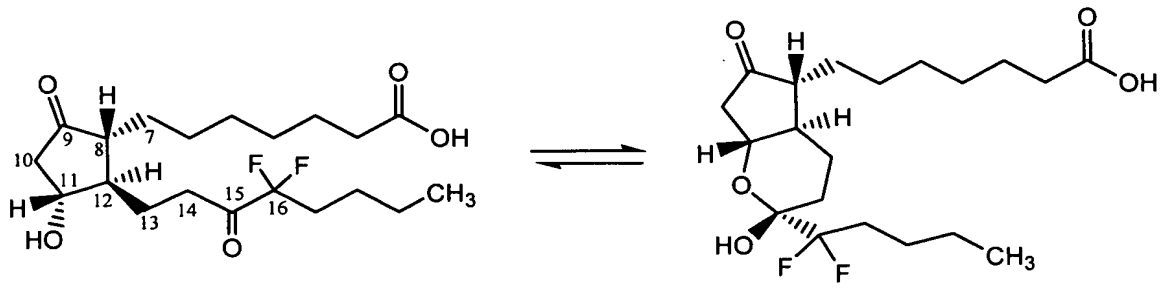
R_3 represents: a hydroxyl or hydroxymethyl group;

R_4 and R_5 each represents: a hydrogen atom, a methyl group or a halogen atom provided that at least one of R_4 and R_5 is a halogen atom; and

R_6 represents: a C_1-C_9 alkyl group which may have a branch or a double bond, or a C_1-C_9 alkyl group having an alkoxy substituent group, the C_2-C_3 bond being a single or double bond.

The applicable patent claims that read on lubiprostone are claims 1-3, 5, 7-9, 11 and 13.

Claim 1 reads on lubiprostone when X is $-CH_2CH_2CH_2-$, R^1 and R^2 are hydrogen atoms, R^3 is a hydroxyl group, R^4 and R^5 are fluorine atoms, R^6 is n-butyl group, the C_2-C_3 bond is a single bond in formula (I), and 8-, 11- and 12-positions have *R* configuration, and this compound is in the form of its tautomeric isomer, where the hydroxyl group at 11-position and the carbonyl group of 15-position combine to form a hemiacetal:



The Applicant notes that the specification defines that the prostaglandin Es of the present invention include isomers of the aforementioned compounds, that examples of these isomers include tautomeric isomers between the hydroxyl group at the 11-position and the carbonyl ground at the 15-position, i.e., a hemiacetal, and that such a tautomreic isomer is easily formed in

a compound having an electron attractive group such as a fluorine atom (see col. 4, lines 49-55). In view of this definition of the prostaglandin compound, the prostaglandin compound recited for the claimed invention includes its tautomer, such that the claimed invention includes within its scope, the tautomer of the prostaglandin compound in addition to the prostaglandin compound itself. The Applicant notes that he may be his own lexicographer by clearly setting forth a definition of a term. *In re Paulsen,* 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994).

Claim 2 reads on lubiprostone for the same reasons as claim 1, where R^4 and R^5 are fluorine atoms.

Claim 3 reads on lubiprostone for the same reasons as claim 2.

Claim 5 reads on lubiprostone for the same reasons as claim 1.

Claim 7 reads on lubiprostone for the same reasons as claim 1.

Claim 8 reads on lubiprostone for the same reasons as claim 2.

Claim 9 reads on lubiprostone for the same reasons as claim 2.

Claim 11 reads on lubiprostone for the same reasons as claim 1.

Claim 13 reads on lubiprostone for the same reasons as claim 1.

(10) A STATEMENT, BEGINNING ON A NEW PAGE, OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. § 156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD.

The relevant dates and information pursuant to 35 U.S.C. 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i)(A) Investigational New Drug Application (IND 59,623) for an oral formulation for the treatment of chronic idiopathic constipation in the adult population was filed with the Food and Drug Administration ("FDA") on December 29, 1999, and became effective on January 29, 2000;

(i)(B) New Drug Application (NDA 21-908) for use of AMITIZA™ as an oral formulation for the treatment of chronic idiopathic constipation in the adult population was submitted to the FDA on March 31, 2005; and

(i)(C) New Drug Application (NDA 21-908) for use of AMITIZA™ as an oral formulation for the treatment of chronic idiopathic constipation in the adult population was approved by the FDA on January 31, 2006. A copy of Patent Information submitted with the filing of an NDA is attached hereto as Exhibit 7.

(11) A BRIEF DESCRIPTION, BEGINNING ON A NEW PAGE, OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES.

DATE TO/FROM FDA	DESCRIPTION
December 29, 1999	Initial IND Application (IND 59,623 for the oral formulation for treatment of chronic idiopathic constipation in the adult population)
January 6, 2000	Receipt of acknowledgement from the FDA
February 23, 2000	Submission of Protocol Amendment: Change in Protocol, New Investigator
March 10, 2000	Receipt of Response to IND Submission
March 10, 2000	Submission of Information Amendment, General Correspondence (Clinical Site Addition, Laboratory Site Addition)
March 28, 2000	Response to FDA RFI (Clinical and CMC Issues)
April 19, 2000	Response to FDA RFI (Efficacy Measures)
April 28, 2000	Submission of Protocol Amendment: Change in Protocol (Primary Endpoint; BMs)
April 28, 2000	Response to FDA RFI
April 28, 2000	Submission of Information Amendment: Chemistry/Microbiology (Stability Data)
September 29, 2000	Meeting Request (Type C (December))
October 17, 2000	Receipt of Denial of Toxicology Meeting Request
November 3, 2000	Submission of Protocol Amendment: New Protocol (PK Study), New Investigator
November 3, 2000	Submission of Information Amendment: Chemistry/Microbiology
December 8, 2000	Receipt of Response to Phase 1 Protocol Amendment
December 14, 2000	Submission of Carcinogenicity Waiver (Long-term Rodent Studies)
December 22, 2000	Submission of Protocol Amendment: Change in Protocol (PK Study)
December 22, 2000	Response to FDA RFI (Formulation Clarification)
January 17, 2001	Request to Submit Type B Meeting
January 24, 2001	Receipt of Confirmation of EOP2 Meeting
March 2, 2001	Submission of Annual Report (1st Annual Report)
March 9, 2001	General Correspondences with the FDA (End of Phase 2 (EOP2) Briefing Package)
April 17, 2001	Response to FDA RFI (EOP2 Meeting Minutes)
April 18, 2001	Request for Type B Meeting (CMC Issues)
April 30, 2001	Receipt of Denial of Request for Waiver

May 7, 2001	Receipt of Confirmation of EOP2 Meeting
May 14, 2001	Receipt of Official Minutes of EOP2 Meeting
May 16, 2001	General Correspondences with the FDA (Clarification of Meeting Minutes)
May 21, 2001	Response to FDA RFI
May 21, 2001	Submission of CMC Meeting Package (Type B CMC Meeting Package)
June 18, 2001	Receipt of Attendee List from EOP2 Meeting
June 28, 2001	General Correspondences with the FDA (Meeting Minutes for EOP3 CMC Meeting)
July 10, 2001	General Correspondence EOP2 CMC Meeting Minutes
July 20, 2001	Teleconference with the FDA
July 24, 2001	General Correspondences with the FDA (Minutes of Conference Call of Pediatrics Discussion, Teleconference Minutes (20 July 2001))
July 26, 2001	General Correspondence Teleconference Minutes
August 1, 2001	Receipt of Official Minutes of CMC EOP2 Minutes
August 17, 2001	Submission of Protocol Amendment: New Protocol (Protocol RTU/0211SC0131)
August 17, 2001	Submission of Information Amendment: Chemistry/Microbiology (Finished Product CMC), Pharmacology/Toxicology (Toxicology Reports)
September 11, 2001	General Correspondences with the FDA (Notification of Intended Carcinogenicity SPA)
October 26, 2001	Request for SPA (Carcinogenicity Protocol)
November 6, 2001	Receipt of Request for Assessment of Carc Study
November 8, 2001	Submission of Protocol Amendment: New Protocol (Protocol RTU/0211SC01S1), Change in Protocol (RTU/0211SC0131), New Investigator
November 8, 2001	Submission of Information Amendment: Chemistry/Microbiology (Dissolution Protocol), Pharmacology/Toxicology (Updated TK data)
November 16, 2001	Submission of Protocol Amendment: New Protocol (Protocol RTU/0211SC01S2)
December 4, 2001	Receipt of Response to Carc SPA Request
December 17, 2001	Response to CAC Report (Dosage Schedule)
December 21, 2001	Receipt of Response to Proposed Carc Study
January 4, 2002	Submission of Protocol Amendment: New Investigator (RTU/0211SC01S1; 01S2)
January 4, 2002	Submission of Information Amendment: Chemistry/Microbiology (Stability Protocol)
February 15, 2002	General Correspondence: Change of Name to SPI
February 26, 2002	Receipt of Receipt of Corporate Name Change

April 30, 2002	Submission of Information Amendment: Pharmacology/Toxicology (3 Reports)
April 30, 2002	Submission of Annual Report (2nd Annual Report)
July 5, 2002	General Correspondence: Protocol Deviation
July 9, 2002	Submission of Protocol Amendment: Change in Protocol (S1 (Amd 1.1.); S2 (Amd 1.1))
August 19, 2002	Submission of Protocol Amendment: New Investigation (SC01S1)
August 19, 2002	Submission of Information Amendment: Pharmacology/Toxicology (Repro Toxicology Protocol)
November 12, 2002	Submission of Protocol Amendment: New Protocol (Protocol RTU/0211SC0232)
January 8, 2003	Receipt of Response to Proposed Monkey Repro Study
January 13, 2003	General Correspondences with the FDA (Request for Clarification of Monkey Species)
February 4, 2003	Submission of Protocol Amendment: New Protocol (Protocol SPI/0211SC02S3)
February 4, 2003	Submission Information Amendment: Clinical (CTR99-004; CTR02-004; IB)
May 30, 2003	Submission of Protocol Amendment: New Investigator (0211SC02S3)
June 5, 2003	Submission of Annual Report (3rd Annual Report)
June 13, 2003	Submission of IND Safety Report: Initial Written Report (Congenital Clubfoot)
June 24, 2003	Submission of IND Safety Report: F/U to a Written Report (Updated CIOMS)
August 22, 2003	Submission of Protocol Amendment: New Investigator (SC0232 and SC02S3)
August 22, 2003	Submission of Information Amendment: Pharmacology/Toxicology, Clinical
August 22, 2003	Submission of Information Amendment: Chemistry/Microbiology (Chemistry Documents)
December 19, 2003	Submission of Information Amendment: Chemistry/Microbiology (^{3}H-0211)
January 16, 2004	Submission of Protocol Amendment: New Protocol (PK Study)
January 23, 2004	Submission of Protocol Amendment; New Investigator (SC0232 and SC02S3)
January 23, 2004	Submission of Information Amendment: Chemistry/Microbiology (^{3}H-0211 COAs), Pharmacology/Toxicology (Toxicology Studies)
February 4, 2004	Submission of Protocol Amendment: Change in Protocol (SPI/0211SA-0312 (Amd 1))
February 16, 2004	Submission of IND Safety Report: Initial Written Report (Diarrhea)
February 27, 2004	Pre-NDA Meeting Request (Type B Meeting (April))

March 19, 2004	Receipt of Denied Abortifacient Meeting Request
March 19, 2004	Receipt of Pre-NDA Meeting Confirmation
March 24, 2004	Teleconference with Dr. Justice
April 26, 2004	Pre-NDA Meeting Pkg (24-May-04 Meeting)
May 5, 2004	Submission of Annual Report: 4th Annual Report
May 14, 2004	General Correspondences with the FDA (Request for List of Attendees at Pre-NDA Meeting)
May 21, 2004	Receipt of Preliminary Pre-NDA Meeting Minutes
May 24, 2004	Receipt of Pre-meeting Response for Meeting
June 8, 2004	Submission of Protocol Amendment New Protocol (QTc Study)
June 8, 2004	Submission of Expedited Review
June 10, 2004	General Correspondence Pre-NDA Meeting Minutes
June 22, 2004	Receipt of Official Minutes of Pre-NDA Meeting; Enclosure
June 23, 2004	Submission of Proprietary Name Review
June 25, 2004	General Correspondences with the FDA (Corrections to FDA meeting Minutes)
July 8, 2004	Submission of Information Amendment: Chemistry/Microbiology (^{3}H-0211 COAs/Stability)
July 8, 2004	Submission of Investigator's Brochure Version 5
July 15, 2004	Receipt of Request for Information (QTc)
August 12, 2004	Submission of Protocol Amendment: Change in Protocol (SPI/0211SC0411 (Amd 1))
November 5, 2004	Response to FDA RFI QTc Study (7/15 Letter)
November 23, 2004	Submission of Protocol Amendment: New Investigator (Protocol SPI/0211SC0411)
February 1, 2005	Response to FDA RFI Biopharm and PK Data
July 8, 2005	Submission of Investigator's Brochure Version 6
December 21, 2005	Submission of Annual Report: 5th Annual Report

March 31, 2005	Original NDA submission
March 31, 2005	Submission of Request for deferral for pediatric studies
March 31, 2005	Submission of Field copy certification to Baltimore District Office
March 31, 2005	Submission of Field copy certification to CDER, FDA
April 11, 2005	Receipt of NDA receipt of acknowledgement (NDA 21-908 assigned)
May 16, 2005	Receipt of RFI: Historical control incidences of tumors (Carcinogenicity studies (rat/mouse))
June 9, 2005	Response to request for CMC information Required for FDA inspection
June 13, 2005	Response to RFI: Tumor data Covance studies

June 13, 2005	Receipt of Filing review (NDA is sufficient for review)
June 21, 2005	Receipt of RFI: Clinical documents Required for FDA inspection
June 23, 2005	Teleconference Clinical documents for inspection
July 1, 2005	Response to RFI: Clinical documents for 4 clinical sites
July 7, 2005	Receipt of Request for carcinogenicity data Biometrics format
July 12, 2005	Applicant Orientation Presentation slides PowerPoint slides (e-mail)
July 18, 2005	Receipt of Timeline for carcinogenicity date filing Mid-August acceptable date
July 21, 2005	Request for waiver and refund of PDUFA Fees (SPI is a small business)
July 27, 2005	4-month safety update report No new safety data
August 6, 2005	Request for Type A meeting Reproductive toxicology issues
August 11, 2005	Receipt of Request for size determination
August 17, 2005	Receipt of Proposed proprietary name
August 23, 2005	Receipt of Type A meeting confirmation (October 5, 2005, 12:00-1:00 P.M.)
September 9, 2005	Information package for Type A meeting 3 publications, PowerPoint
September 11, 2005	Receipt of Type A meeting details Format of presentation
September 13, 2005	Receipt of SBA/Formal size determination Small business confirmation
September 16, 2005	Submission of Carcinogenicity data Biometrics format
September 30, 2005	Submission of Packaging site; process parameter revised tox report 3-part submission
October 4, 2005	Receipt of Response to Type A meeting questions (3 questions)
October 14, 2005	Submission of Type A meeting presentation materials
October 31, 2005	Receipt of PDUFA fee waiver/refund Waiver/refund granted
November 2, 2005	Receipt of Type A meeting minutes "Review is ongoing"
November 10, 2005	Receipt of PREA discussion (Request for pediatric assessment)
November 16, 2005	Submission of 36-month stability data for capsules HDPE bottles and blister pack
November 22, 2005	Receipt of Rejection of proprietary name "Etreva"
December 7, 2005	Submission of Proposed proprietary name "Amitiza"
December 7, 2005	Submission of Revised 4-month safety update report (Dates specified)
December 9, 2005	Receipt of Discipline Response Letter (DMF deficiency)
December 21, 2005	Response to Discipline Response Letter (DMF deficiency resolved)
December 23, 2005	Receipt of RFI: Revision to Figure 1 labeling (Median SBM values requested)
January 3, 2006	Response to RFI: Figure 1 labeling (Median SBM values prepared)
January 12, 2006	Receipt of RFI: Revision to Figure 1 labeling (Interquartile ranges requested)
January 13, 2006	Receipt of 1st FDA revision to labeling text and packaging (Label negotiations)

January 18, 2006	Receipt of 2nd FDA revision to labeling text (Label negotiations)
January 19, 2006	Submission of 1st SPI revision to labeling text (Label negotiations)
January 22, 2006	Submission of 1st SPI revision to packaging (Label negotiations)
January 23, 2006	Submission of 1st SPI revision to packaging follow-up (Label negotiations)
January 24, 2006	Receipt of 3rd (Final) FDA revision to labeling text (Label negotiations)
January 24, 2006	Receipt of 2nd FDA revision to packaging (Label negotiations)
January 25, 2006	Submission of 2nd SPI revision to labeling text (Label negotiations)
January 25, 2006	Submission of 2nd SPI revision to packaging (Label negotiations)
January 25, 2006	Response to RFI: Figure 1; revised labeling (Label negotiations)
January 25, 2006	Submission of Other AE listing revision (Proposed revision to labeling)
January 26, 2006	Teleconference with the FDA (Final label negotiations)
January 26, 2006	Receipt of Post-marketing commitments request (Pediatrics; renal; hepatic)
January 26, 2006	Submission of Country of origin on packaging query (Proposed text)
January 26, 2006	Receipt of Other AE listing revision (To be submitted as supplement)
January 27, 2006	Receipt of 3rd (Final) FDA revision to packaging (Agreement letter requested)
January 27, 2006	Submission of Revised Figure 1 of labeling
January 27, 2006	Submission of 3rd (Final) SPI revision to labeling; PMC letter
January 27, 2006	Submission of 3rd (Final) SPI revision to packaging
January 27, 2006	Receipt of Country of origin on packaging
January 28, 2006	3rd (Final) SPI revision to packaging follow-up
January 30, 2006	Submission of post-marketing commitments update
January 31, 2006	Receipt of NDA approval letter (NDA 21-908)
January 31, 2006	NDA approval letter acknowledgement via fax
February 2, 2006	Submission of final labeling and post-marketing commitment letter
February 8, 2006	Authorization for TPNA to submit to DDMAC
February 27, 2006	Submission of patent listing (Orange Book) for Amitiza
March 9, 2006	Submission of IND 59,623 Annual Report

(12) A STATEMENT, BEGINNING ON A NEW PAGE, THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED.

The Applicant is of the opinion that U.S. Patent 5,284,858 is eligible for the extension of patent term applied for under 35 U.S.C. § 156 because it satisfies all the requirements for such extension as follows.

(a) 35 U.S.C. § 156(a)

U.S. Patent 5,284,858 claims a product and a method of using the claimed product that encompass lubiprostone.

(b) 35 U.S.C. § 156(a) (1)

The term of U.S. Patent 5,284,858 expires February 8, 2011 as measured seventeen (17) years from the issue date, and thus, has not expired before submission of this application.

(c) 35 U.S.C. § 156(a) (2)

The term of U.S. Patent 5,284,858 has never been extended.

(d) 35 U.S.C. § 156(a) (3)

The application for extension is submitted by the authorized agent of the owner of record in accordance with the requirements of 35 U.S.C. § 156(d) and the rules of the U.S. Patent and Trademark Office. A copy of a duly executed Power of Attorney and Appointment of Agent is attached hereto as Exhibit 8.

(e) 35 U.S.C. § 156(a) (4)

The product, AMITIZA™ (Lubiprostone) Soft Gelatin Capsules, has been subjected to a regulatory review period as defined in 35 U.S.C. § 156(g) before its commercial marketing or use.

(f) 35 U.S.C. § 156(a) (5) (A)

The commercial marketing or use of the product, AMITIZA™ (Lubiprostone) Soft Gelatin Capsules, after the regulatory review period is the first permitted commercial marketing or use of the product under the provisions of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 355, under which said regulatory review period occurred.

(g) 35 U.S.C. § 156(c) (4)

No other patent has been extended for the same regulatory review period for the product, AMITIZA™ (Lubiprostone) Soft Gelatin Capsules.

(12-A) The length of extension of the patent term of U.S. Patent 5,284,858 claimed by the Applicant is **1251 days**. The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g) (1) (B) began on January 29, 2000, and ended on January 31, 2006, which is a total of 2195 days, which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. § 156(g) (1) (B) (i), the "testing period," began on January 29, 2000 and ended on March 31, 2005, which is 1888 days; and

(ii) The period of review under 35 U.S.C. § 156(g) (1) (B) (ii), the "application period," began on March 31, 2005 and ended on January 31, 2006, which is 307 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph (12-A) (a) above (2195 days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (February 8, 1994) which is zero (0) days, and

(ii) The number of days in which the Applicant did not act with due diligence which is zero (0) days, and

(iii) One-half the number of days determined in subparagraph (12-A) (a) (i) less (b)(i) and (ii) above, or (1888 - 0 - 0) x ½ = 944 days,

which totals 1251 days;

(c) The number of days as determined in subparagraph (12-A) (b) (1251 days) when added to the original term of the patent would result in the date, July 13, 2014;

(d) Fourteen (14) years when added to the date of NDA approval (January 31, 2006), result in the date, January 31, 2020;

(e) The earlier date as determined in subparagraphs (12-A) (c) and (12-A) (d) is July 13, 2014;

(f) The original patent was issued after September 24, 1984. Therefore, five (5) years when added to the original expiration date of the patent (February 8, 2011) would result in the date, February 8, 2016:

(g) The earlier date as determined in subparagraph (12-A) (e) and (12-A) (f) is July 13, 2014.

Therefore, the length of extension of patent term claimed by the Applicant is 1251 days. The date of termination of the extended patent term is not more than 14 years from the date of NDA approval.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT.

The Applicant acknowledges a duty to disclose to the Commissioner of Patent and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION.

The prescribed fee for receiving and acting upon this application is to be charged to the deposit account of the Applicant's agent as authorized in the attached letter, which is submitted in duplicate.

(15) THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED.

All inquires and correspondence should be directed to Bruce E. Kramer and Fang Liu, Ph.D., SUGHRUE MION, PLLC, 2100 Pennsylvania Ave., NW, Suite 800, Washington, D.C. 20037-3213, telephone number (202) 293-7060.

(16) FOUR ADDITIONAL COPIES OF THE APPLICATION PAPERS.

Four duplicates of these Application papers are enclosed as Exhibit 9.

Respectfully submitted,

Bruce E. Kramer
Registration No. 33,725

Fang Liu, Ph.D.
Registration No. 51,283

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: March 27, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 5,284,858

Docket No: Q29894 (ID004406)

Issued: February 8, 1994

Assignee: Sucampo AG

For: PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME

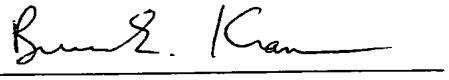
AUTHORIZATION TO CHARGE DEPOSIT ACCOUNT

MAIL STOP: Patent Term Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The USPTO is directed and authorized to charge the statutory fee of $1,120.00, as well as any other required fees, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account. A duplicate copy of this paper is attached.

Respectfully submitted,



Bruce E. Kramer
Registration No. 33,725

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: March 27, 2006

Assignment

SERIAL NO. _____ FILED _____

In consideration of the sum of One Dollar ($1.00) and other good and valuable consideration, the receipt of which is hereby acknowledged,

Insert Name(s) of Inventor(s)

Ryuzo UENO, Ryuji UENO, Ichie Kato and Tomio ODA

(hereinafter designated as the undersigned) hereby sell(s) and assign(s) to

Insert Name of Assignee

KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO

Address of Assignee

of 4-8, 2-chome, Koraibashi, Chuo-ku, Osaka-shi, Osaka-fu, Japan ,

its heirs, successors, legal representatives and assigns (hereinafter designated as the Assignee), the entire right, title and interest in the invention or improvements in

Title of Invention

PROSTAGLANDINS E AND ANTI-ULCERS CONTAINING SAME

for which an application for Letters Patent of the United States of America has been executed by the undersigned

Date of Signing of Application

on September 28, 1989 and September 26, 1989 respectively

The undersigned agree(s) to execute all papers necessary in connection with this application and any continuing, divisional or reissue applications thereof and also to execute separate assignments in connection with such applications as the Assignee may deem necessary or expedient.

The undersigned agree(s) to execute all papers necessary in connection with any interference which may be declared concerning this application or continuation, division or reissue thereof or letters patent or reissue patent issued thereon and to cooperate with the Assignee in every way possible in obtaining and producing evidence and proceeding with such interference.

The undersigned agree(s) to execute all papers and documents and to perform any act which may be necessary in connection with claims or provisions of the International Convention for the Protection of Industrial Property or similar agreements.

The undersigned agree(s) to perform all affirmative acts which may be necessary to obtain a grant of a valid United States patent to the Assignee and to vest all rights therein hereby conveyed to said Assignee as fully and entirely as the same would have been held by the undersigned if this assignment and sale had not been made.

The undersigned hereby authorize(s) and request(s) the Commissioner of Patents to issue any and all Letters Patents of the United States resulting from said application or any division or divisions or continuing or reissue applications thereof to the said Assignee, as Assignee of the entire interest, and hereby covenants that he has (they have) the full right to convey the entire interest herein assigned, and that he has (they have) not executed, and will not execute, any agreement in conflict herewith.

In witness whereof, executed by the undersigned on the date(s) opposite the undersigned name(s).

Date Sep. 28, 1989 , Name of Inventor _____ (signature)

Date Sep. 26, 1989 , Name of Inventor _____ (signature)

Date Sep. 28, 1989 , Name of Inventor _____ (signature)

Date Sep. 28, 1989 , Name of Inventor _____ (signature)

Date _____ , Name of Inventor _____ (signature)

(This assignment should preferably be acknowledged before a United States Consul or Notary Public. If not, then the execution by the Inventor(s) should be witnessed by at least two other persons who sign here.)

Witness _____

Witness _____

Witness _____

ACKNOWLEDGMENT

_____ }
_____ }

On this _____ day of _____ , 19 ____, before me

personally appeared the above-named _____

_____

_____

to me personally known to be the individual(s) who executed the foregoing assignment, who did acknowledge to me that he (they) executed the same of his (their) own free will for the purposes therein set forth.

Witness my hand and seal the day and year last above given.

RECORDED
PATENT & TRADEMARK OFFICE
OCT 18 89

_____
Official Signature

(SEAL)

_____
Official Title

COMMISSIONER OF PATENTS AND TRADEMARKS OFFICE

ASSIGNMENT

Whereas, Kabushiki Kaisha Ueno Seiyaku Oyo Kenkyujo, a Corporation of Japan, 4-8, Koraibashi, 2-chome, Chuo-ku, Osaka-shi, Osaka-fu, Japan, is the sole owner by Assignment of the following United States Letters Patents and pending application:

U.S. Patent 5,166,174 - Issued November 24, 1992 (USSN 07/700,895)
U.S. Patent 5,225,439 - Issued July 6, 1995 (USSN 07/681,031)
U.S. Patent 5,284,858 - Issued February 8, 1994 (USSN 07/925,220)
U.S. Patent 5,380,709 - Issued January 10, 1995 (USSN 08/053,561)
U.S. Patent 5,428,062 - Issued June 27, 1995 (USSN 08/053,487)
U.S. Patent 5,886,034 - Issued March 23, 1999 (USSN 08/401,675)
U.S. Patent 5,317,032 - Issued May 31, 1994 (USSN 07/996,495)
Pending U.S. Application 09/073,253, filed May 6, 1998

Whereas SUCAMPO AG, a Corporation of Switerzland, having a business address at Graben 5,. CH-6300, Zug , Switerzland is desirous of acquiring all rights, title, and interest in and to the aforesaid Letters Patents of the United States, any reissue of any such patent and said pending United States patent application:

Now therefore, for valuable consideration, receipt whereof is hereby acknowledged,

KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO as Assignor, hereby sells, assigns and transfers to the aforesaid SUCAMPO AG, its successors and assigns, the entire right, title and interest in and to the above-named patents, any reissue of any such patent and said pending patent application.

AND said KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO hereby agrees upon request to execute any instrument which SUCAMPO AG desires to carry this Assignment into effect and perfect the title transferred hereby.

IN TESTIMONY WHEREOF the Assignor has executed these presents.

Signed on May 15, 2001

KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO
By: Ryuzo Ueno
Name: Ryuzo UENO
Title: President
KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO

6/15 ST ANNA

8/30 Recvd

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

AUGUST 25, 2001

PTAS

101753190A

SUGHRUE, MION, ZINN, MACPEAK & SEAS,PLLC
LOUIS GUBINSKY
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, D.C. 20037-3213

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 06/13/2001

REEL/FRAME: 011887/0481
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR''S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO

DOC DATE: 05/15/2001

ASSIGNEE:
SUCAMPO AG
GRABEN 5, CH-6, SWITZERLAND

SERIAL NUMBER: 09073253
PATENT NUMBER: 6265440

FILING DATE: 05/06/1998
ISSUE DATE: 07/24/2001

SERIAL NUMBER: 07700895
PATENT NUMBER: 5166174

FILING DATE: 05/13/1991
ISSUE DATE: 11/24/1992

SERIAL NUMBER: 07681031
PATENT NUMBER: 5225439

FILING DATE: 04/05/1991
ISSUE DATE: 07/06/1993

SERIAL NUMBER: 07925220
PATENT NUMBER: 5284858

FILING DATE: 08/06/1992
ISSUE DATE: 02/08/1994

SERIAL NUMBER: 08053561	FILING DATE: 04/28/1993
PATENT NUMBER: 5380709	ISSUE DATE: 01/10/1995
SERIAL NUMBER: 08053487	FILING DATE: 04/28/1993
PATENT NUMBER: 5428062	ISSUE DATE: 06/27/1995
SERIAL NUMBER: 08401675	FILING DATE: 03/10/1995
PATENT NUMBER: 5886034	ISSUE DATE: 03/23/1999
SERIAL NUMBER: 07996495	FILING DATE: 12/30/1992
PATENT NUMBER: 5317032	ISSUE DATE: 05/31/1994

TARA WASHINGTON, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

EXHIBIT 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of:

Ryuzo UENO, et al. Docket No: 004406

U.S. Patent No.: 5,284,858

Issued: February 8, 1994

For: PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME

LETTER AUTHORIZING RELIANCE ON ACTIVITY BEFORE THE FDA IN ASSOCIATION WITH APPLICATION FOR PATENT TERM EXTENSION

UNDER 35 U.S.C. § 156

MAIL STOP: Patent Term Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

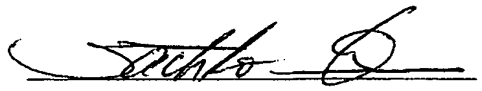
Sucampo Pharmaceuticals, Inc. is the owner of IND 59,623 and NDA 21-908, filed for the approval of the approved product AMITIZA™ (lubiprostone) Soft Gelatin Capsules.

Sucampo Pharmaceuticals, Inc. was the marketing applicant before the FDA during the regulatory review period for IND 59,623 and NDA 21-908. During the regulatory review period for IND 59,623 and NDA 21-908, Sucampo Pharmaceuticals, Inc. had an agency relationship with Sucampo AG of Switzerland.

The undersigned hereby authorizes the applicant for patent term extension, Sucampo AG, to rely on the activities before the FDA pursuant to IND 59,623 and NDA 21-908 in association with the approval of AMITIZA™ (lubiprostone) Soft Gelatin Capsules.

Date: March 10, 2006

Sucampo Pharmaceuticals, Inc.

By: 

Name: Sachiko Kuno, PhD
Title: President and CEO

EXHIBIT 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-908

Sucampo Pharmaceuticals, Inc.
4733 Bethesda Avenue, Suite 450
Bethesda, Maryland 20814

REC'D FEB 03 2006

Dear Dr. Cormack:

Please refer to your new drug application (NDA) dated March 31, 2005, received March 31, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amitiza™ (Lubiprostone Capsules).

We acknowledge receipt of your submissions dated June 9, July 27, September 16, September 30, October 17, November 2, November 16, November 22, December 7, December 9, December 14, December 21, December 23, 2005 and January 3, 2006.

This new drug application provides for the use of Amitiza™ (Lubiprostone Capsules) for the treatment of chronic idiopathic constipation in the adult population.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling and submitted labeling (package insert submitted January 27, 2006 and immediate container and carton labels submitted January 28, 2006). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0 to 17 years until January 31, 2008.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

Deferred pediatric studies under PREA for the treatment of chronic idiopathic constipation in pediatric patients ages 0 to 17 years.

Protocol Submission:	by July 31, 2006
Study Start:	by January 31, 2007
Final Report Submission:	by January 31, 2008

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

We remind you of your postmarketing study commitments in your submission dated January 27, 2006. These commitments are listed below.

1. Perform a Phase IV study to assess the need for potential dose adjustment in patients with renal impairment.

Protocol Submission:	by July 31, 2006
Study Start:	by January 31, 2007
Final Report Submission:	by January 31, 2008

2. Perform a Phase IV study to assess the need for potential dose adjustment in patients with hepatic impairment.

Protocol Submission:	by July 31, 2006
Study Start:	by January 31, 2007
Final Report Submission:	by January 31, 2008

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Tanya Clayton, B.S., Regulatory Health Project Manager at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Acting Director
Office of New Drug Evaluation III
Center for Drug Evaluation and Research

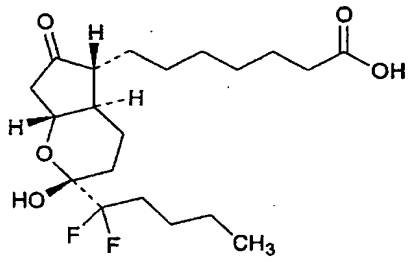
Enclosure

AMITIZA™
(lubiprostone)
Soft Gelatin Capsules

Rx Only, Prescribing Information

DESCRIPTION

AMITIZA™ (lubiprostone) is chemically designated as (–)-7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid. The molecular formula of lubiprostone is $C_{20}H_{32}F_2O_5$ with a molecular weight of 390.46 and a chemical structure as follows:



Lubiprostone drug substance occurs as white, odorless crystals or crystalline powder and is very soluble in ether and ethanol, and practically insoluble in hexane and water. AMITIZA™ is available for oral administration in an imprinted, oval, orange, soft gelatin capsule containing 24 mcg lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, FD&C Red #40, D&C Yellow #10, and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Chronic idiopathic constipation is generally defined by infrequent or difficult passage of stool. The signs and symptoms associated with chronic idiopathic constipation (*i.e.*, abdominal pain or discomfort, bloating, straining, and hard or lumpy stools) may be the result of abnormal colonic motility that can delay the transit of intestinal contents and impede the evacuation of rectal contents. One approach to the treatment of chronic idiopathic constipation is the secretion of fluid into the

abdominal lumen through the activation of chloride channels in the apical membrane of the gastrointestinal epithelium.

Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating ClC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A–independent fashion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. Patch clamp cell studies in human cell lines have indicated that the majority of the beneficial biological activity of lubiprostone and its metabolites is observed only on the apical (luminal) portion of the gastrointestinal epithelium.

Pharmacokinetics:

Lubiprostone has low systemic availability following oral administration and concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/mL). Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), C_{max}, and $t_{½}$ cannot be reliably calculated. However, the pharmacokinetic parameters of M3 (only measurable active metabolite) have been characterized.

Absorption:

Concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/mL) because lubiprostone has a low systemic availability following oral administration. Peak plasma levels of M3, after a single oral dose of 24 mcg of lubiprostone, occur at approximately 1.14 hours. The C_{max} was 41.9 pg/mL and the mean AUC was 59.1 pg•hr/mL. AUC of M3 increases dose proportionally after single 24-mcg and 144-mcg doses of lubiprostone.

Distribution:

In vitro protein binding studies indicate lubiprostone is approximately 94% bound to human plasma proteins. Studies in rats with radiolabeled lubiprostone indicate minimal distribution beyond the gastrointestinal tissues. Concentrations of radiolabeled compound at 48 hours post-administration were minimal in all tissues.

Metabolism:

The results of both human and animal studies indicate that lubiprostone is rapidly and extensively metabolized by 15-position reduction, α-chain β-oxidation, and ω-chain ω-oxidation. These biotransformations are not mediated by the hepatic cytochrome P450 system but rather appear to be mediated by the ubiquitously expressed carbonyl reductase. M3, a metabolite of lubiprostone in both humans and animals is formed by the reduction of the carbonyl group at the 15-hydroxy moiety that consists of both α-hydroxy and β-hydroxy epimers. M3 makes up less than 10% of the dose of radiolabeled lubiprostone. Animal studies have shown that metabolism of lubiprostone rapidly occurs within the stomach and jejunum, most likely in the absence of any systemic absorption. This is presumed to be the case in humans as well.

Elimination:

Lubiprostone could not be detected in plasma; however, M3 has a $t_{½}$ ranging from 0.9 to 1.4 hours. After a single oral dose of 72 mcg of ^{3}H-labeled lubiprostone, 60% of total administered radioactivity was recovered in the urine within 24 hours and 30% of total administered radioactivity was recovered in the feces by 168 hours. Lubiprostone and M3 are only detected in trace amounts in feces in humans.

Food Effect:

A study was conducted with a single 72-mcg dose of ^{3}H-labeled lubiprostone to evaluate the potential of a food effect on lubiprostone absorption, metabolism, and excretion (AME). Pharmacokinetic parameters of total radioactivity demonstrated that C_{max} decreased by 55% while $AUC_{0-\infty}$ was unchanged when lubiprostone was administered with a high-fat meal. The clinical relevance of the effect of food on the pharmacokinetics of lubiprostone is not clear. However, lubiprostone was administered with food in a majority of clinical trials.

Special Populations:

Gender:

Gender has no effect on the pharmacokinetics of M3 when lubiprostone is dosed.

Hepatic Impairment:

Lubiprostone has not been studied in hepatically impaired populations.

Renal Impairment:

Lubiprostone has not been studied in renally impaired populations.

CLINICAL STUDIES

A dose-finding, double-blind, parallel-group, placebo-controlled, Phase 2 study was conducted in patients with chronic idiopathic constipation. Following a 2-week baseline/washout period, patients received 3 weeks of double-blind medication. Patients (n = 127) were randomized to receive placebo (n = 33), AMITIZA™ 24 mcg/day (24 mcg QD; n = 29), AMITIZA™ 48 mcg/day (24 mcg BID; n = 32), or AMITIZA™ 72 mcg/day (24 mcg TID; n = 33). Patients were chosen for participation based on their need for relief of constipation, which was defined as < 3 spontaneous bowel movements (SBMs) per week. The primary efficacy variable was the daily average number of SBMs.

The study demonstrated that all patients who took AMITIZA™ experienced a noticeable improvement in clinical response. Based on the efficacy analysis, there was no statistically significant improvement in the clinical response beyond a total daily dose of 24 mcg between treatment weeks 2 and 3 (Figure 1).

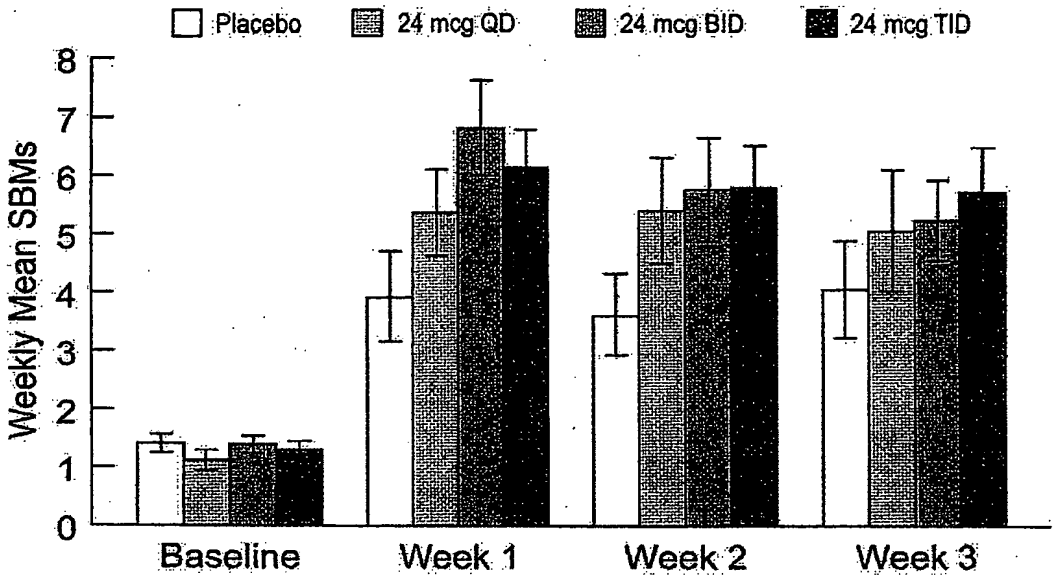


Figure 1: Weekly Mean (± Standard Error) Spontaneous Bowel Movements (Dose-finding Study)

Two double-blind, placebo-controlled studies of identical design were conducted in patients with chronic idiopathic constipation. Chronic idiopathic constipation was defined as, on average, less than 3 SBMs per week with one or more of the following symptoms for constipation for at least 6 months prior to randomization: 1) very hard stools for at least a quarter of all bowel movements; 2) sensation of incomplete evacuation following at least a quarter of all bowel movements; and 3) straining with defecation at least a quarter of the time.

Following a 2-week baseline/washout period, a total of 479 patients (88.9% female, mean age 47.2 [range 20.0–81.0], 80.8% Caucasian, 9.6% African American, 10.9% ≥ 65 years of age) were randomized to receive 4 weeks of double-blind treatment with either AMITIZA™ 24 mcg BID (48 mcg/day) or placebo. The primary endpoint of the studies was SBM frequency following initiation of double-blind treatment. The studies demonstrated that patients treated with AMITIZA™ had a higher frequency of SBMs during Week 1 than the placebo patients. In both studies, results similar to those in Week 1 were also observed in Weeks 2, 3, and 4 of therapy.

Table 1: Spontaneous Bowel Movement Frequency Rates – AMITIZA™ 24 mcg BID vs. Placebo

Trial	Study Arm	Baseline *Mean ± SD Median*	Week 1 *Mean ± SD Median*	Week 2 *Mean ± SD Median*	Week 3 *Mean ± SD Median*	Week 4 *Mean ± SD Median*	Week 1 Change from Baseline *Mean ± SD Median*	Week 4 Change from Baseline *Mean ± SD Median*
Study 1	Placebo	1.6 ± 1.3 1.5	3.5 ± 2.3 3.0	3.2 ± 2.5 3.0	2.8 ± 2.2 2.0	2.9 ± 2.4 2.3	1.9 ± 2.2 1.5	1.3 ± 2.5 1.0
	AMITIZA™	1.4 ± 0.8 1.5	5.7 ± 4.4 5.0	5.1 ± 4.1 4.0	5.3 ± 4.9 5.0	5.3 ± 4.7 4.0	4.3 ± 4.3 3.5	3.9 ± 4.6 3.0
Study 2	Placebo	1.5 ± 0.8 1.5	4.0 ± 2.7 3.5	3.6 ± 2.7 3.0	3.4 ± 2.8 3.0	3.5 ± 2.9 3.0	2.5 ± 2.6 1.5	1.9 ± 2.7 1.5
	AMITIZA™	1.3 ± 0.9 1.5	5.9 ± 4.0 5.0	5.0 ± 4.2 4.0	5.6 ± 4.6 5.0	5.4 ± 4.8 4.3	4.6 ± 4.1 3.8	4.1 ± 4.8 3.0

The above frequency rates are calculated as 7 times (number of SBMs) / (number of days observed for that week).

In both studies, AMITIZA™ demonstrated increases in the percentage of patients who experienced SBMs within the first 24 hours after administration when compared to placebo (56.7% vs. 36.9% in Study 1 and 62.9% vs. 31.9% in Study 2, respectively). Similarly, the time to first SBM was shorter for AMITIZA™ patients than for those receiving placebo.

Signs and symptoms related to constipation, including abdominal bloating, abdominal discomfort, stool consistency, and straining, as well as constipation severity ratings, were also improved in AMITIZA™ patients versus placebo. The results were consistent in subpopulation analysis for gender, race, and elderly patients (≥ 65 years of age).

Following 4 weeks of treatment with AMITIZA™ 24 mcg BID, withdrawal of AMITIZA™ did not result in a rebound effect.

Long-term Clinical Studies:

Three open-label, long-term clinical safety studies were conducted in patients with chronic idiopathic constipation receiving 24 mcg BID. These studies included 871 patients (86.1% female, mean age 51 [range 19–86] years, 87% Caucasian, 7.3% African American, 18.4% ≥ 65 years of age) who were treated for 6–12 months (24–48 weeks). Patients provided regular assessments of abdominal bloating, abdominal discomfort, and constipation severity. The results of these studies demonstrated that AMITIZA™ decreased abdominal bloating, abdominal discomfort, and constipation severity over the 6–12 month treatment periods.

INDICATION AND USAGE

AMITIZA™ is indicated for the treatment of chronic idiopathic constipation in the adult population.

CONTRAINDICATION

AMITIZA™ is contraindicated in those patients with a known hypersensitivity to the drug or any of its excipients, and in patients with a history of mechanical gastrointestinal obstruction.

WARNING

Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be evaluated prior to initiating AMITIZA™ treatment.

The safety of AMITIZA™ in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to have the potential to cause fetal loss. AMITIZA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with AMITIZA™ and should be capable of complying with effective contraceptive measures (see TERATOGENIC EFFECTS: PREGNANCY CATEGORY C).

PRECAUTIONS

Patient Information:

AMITIZA™ may cause nausea. If this occurs, concomitant administration of food with AMITIZA™ may reduce symptoms of nausea. AMITIZA™ should not be administered to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. If the diarrhea becomes severe consult your physician.

Drug Interactions:

Based upon the results of *in vitro* human microsome studies, there is low likelihood of drug–drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to M3. Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit

cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies in primary cultures of human hepatocytes show no induction of the cytochrome P450 isoforms 1A2, 2B6, 2C9 and 3A4. No additional drug–drug interaction studies have been performed. Based on the available information, no protein binding–mediated drug interactions of clinical significance are anticipated.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis:

Two 2-year oral (gavage) carcinogenicity studies (one in Crl:B6C3F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the 2-year carcinogenicity study in mice, lubiprostone doses of 25, 75, 200, and 500 mcg/kg/day (approximately 2, 6, 17, and 42 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, lubiprostone doses of 20, 100, and 400 mcg/kg/day (approximately 3, 17, and 68 times the recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidences. There was a significant increase in the incidence of interstitial cell adenoma of the testes in male rats at the 400 mcg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 mcg/kg/day dose.

Lubiprostone was not genotoxic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma (L5178Y TK+/–) forward mutation assay, the *in vitro* Chinese hamster lung (CHL/IU) chromosomal aberration assay, and the *in vivo* mouse bone marrow micronucleus assay.

Lubiprostone, at oral doses of up to 1000 mcg/kg/day, had no effect on the fertility and reproductive function of male and female rats. The 1000 mcg/kg/day dose in rats is approximately 166 times the recommended human dose of 48 mcg/day, based on the body surface area.

TERATOGENIC EFFECTS: PREGNANCY CATEGORY C

Teratology studies with lubiprostone have been conducted in rats at oral doses up to 2000 mcg/kg/day (approximately 332 times the recommended human dose, based on body surface area), and in rabbits at oral doses of up to 100 mcg/kg/day (approximately 33 times the recommended human dose, based on body surface area). Lubiprostone was not teratogenic in rats and rabbits. In guinea pigs, lubiprostone

caused fetal loss at repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the human dose, respectively, based on body surface area) administered on days 40 to 53 of gestation.

There are no adequate and well-controlled studies in pregnant women. However, during clinical testing of AMITIZA™ at 24 mcg BID, four women became pregnant. Per protocol, AMITIZA™ was discontinued upon pregnancy detection. Three of the four women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the patient was subsequently lost to follow-up.

AMITIZA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman is or becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers:
It is not known whether lubiprostone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lubiprostone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
AMITIZA™ has not been studied in pediatric patients.

Renal Impaired:
AMITIZA™ has not been studied in patients who have renal impairment.

Hepatic Impaired:
AMITIZA™ has not been studied in patients who have hepatic impairment.

ADVERSE REACTIONS
In clinical trials, 1429 patients received AMITIZA™ 24 mcg BID or placebo. Table 2 presents data for the adverse experiences that were reported in at least 1% of patients who received AMITIZA™ and that occurred more frequently on study drug than placebo. It should be noted that the placebo data presented are from short-term exposure (≤4 weeks) whereas the AMITIZA™ data are cumulative data

that were collected over 3- or 4-week, 6-month and 12-month observational periods and that some conditions are common among otherwise healthy patients over a 6- and 12-month observational period.

Table 2: Adverse Events Reported for Patients Treated with AMITIZA™

System/Adverse Experience	Placebo n = 316 %	AMITIZA™ 24 mcg QD n = 29 %	AMITIZA™ 24 mcg BID n = 1113 %	AMITIZA™ Any Active Dose[1] n = 1175 %
Gastrointestinal disorders				
Nausea	5.1	17.2	31.1	30.9
Diarrhea	0.9	10.3	13.2	13.2
Abdominal distension	2.2	0.0	7.1	6.8
Abdominal pain	2.8	3.4	6.7	6.8
Flatulence	1.9	3.4	6.1	5.9
Vomiting	0.9	0.0	4.6	4.4
Loose stools	0.0	0.0	3.4	3.2
Dyspepsia	1.3	0.0	2.9	2.7
Abdominal pain upper	1.9	0.0	2.2	2.1
Abdominal pain lower	0.6	0.0	1.9	1.8
Gastroesophageal reflux disease	0.6	0.0	1.8	1.7
Abdominal discomfort	0.0	3.4	1.5	1.5
Dry mouth	0.3	0.0	1.5	1.4
Constipation	0.9	0.0	1.1	1.0
Stomach discomfort	0.3	0.0	1.1	1.0
Infections and infestations				
Sinusitis	1.6	0.0	4.9	4.8
Urinary tract infections	1.9	3.4	4.4	4.3
Upper respiratory tract infection	0.9	0.0	3.7	3.6
Nasopharyngitis	2.2	0.0	2.9	2.7
Influenza	0.6	0.0	2.0	1.9
Bronchitis	0.3	3.4	1.6	1.7
Gastroenteritis viral	0.0	3.4	1.0	1.0
Viral infection	0.3	3.4	0.5	0.6
Nervous system disorders				
Headache	6.6	3.4	13.2	13.0
Dizziness	1.3	3.4	4.1	4.0
Hypoesthesia	0.0	3.4	0.5	0.6
General disorders and site administration conditions				
Edema peripheral	0.3	0.0	3.8	3.6
Fatigue	1.9	6.9	2.3	2.5
Chest discomfort	0.0	3.4	1.6	1.6
Chest pain	0.0	0.0	1.1	1.0
Pyrexia	0.3	0.0	1.1	1.0
Musculoskeletal and connective tissue disorders				
Arthralgia	0.3	0.0	3.1	3.0
Back pain	0.9	3.4	2.3	2.3
Pain in extremity	0.0	3.4	1.9	1.9
Muscle cramp	0.0	0.0	1.0	0.9
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	0.0	3.4	2.4	2.5
Pharyngolaryngeal pain	2.2	0.0	1.7	1.6
Cough	0.6	0.0	1.6	1.5
Investigations				
Weight increased	0.0	0.0	1.0	0.9
Psychiatric disorders				
Depression	0.0	0.0	1.4	1.4
Anxiety	0.3	0.0	1.4	1.4
Insomnia	0.6	0.0	1.4	1.4

Vascular disorders				
Hypertension	0.0	0.0	1.0	0.9

[1]Includes patients dosed at 24 mcg QD, 24 mcg BID, and 24 mcg TID

AMITIZA ™-induced Nausea:

Among constipated patients, 31.1% of those receiving AMITIZA™ 24 mcg BID reported nausea. Of those patients, 3.4% reported severe nausea and 8.7% discontinued treatment due to nausea. It should be noted that the incidence of nausea increased in a dose-dependent manner with the lowest overall incidence for nausea seen at the 24 mcg QD dose (17.2%). Further analysis of nausea has shown that long-term exposure to AMITIZA™ does not appear to place patients at elevated risk for experiencing nausea. In the open-label, long-term studies, patients were allowed to titrate the dose of AMITIZA™ down to 24 mcg QD from 24 mcg BID if experiencing nausea. It should also be noted that nausea decreased when AMITIZA™ was administered with food and that, across all dose groups, the rate of nausea was substantially lower among constipated men (13.2%) and constipated elderly patients (18.6%) when compared to the overall rate (30.9%). No patients in the trials were hospitalized due to nausea.

AMITIZA ™-induced Diarrhea:

Among constipated patients, 13.2% of those receiving AMITIZA™ 24 mcg BID reported diarrhea. Of those patients, 3.4% reported severe diarrhea and 2.2% discontinued treatment due to diarrhea. The incidence of diarrhea did not appear to be dose-dependent. No serious adverse events were reported for electrolyte imbalance in the six clinical trials and no clinically significant changes were seen in serum electrolyte levels while patients were receiving AMITIZA™.

Other Adverse Events:

The following list of adverse events include those that were considered by the investigator to be possibly related to AMITIZA™ and reported more frequently (>0.2%) on AMITIZA™ than placebo and those that lead to discontinuation more frequently (≥0.2%) on AMITIZA™ than placebo. Although the events reported occurred during treatment with AMITIZA™, they were not necessarily attributed to dosing of AMITIZA™:

- **Gastrointestinal disorders:** watery stools, fecal incontinence, abnormal bowel sounds, frequent bowel movements, retching

- **Nervous system disorders:** syncope, tremor, dysgeusia, paraesthesia
- **General disorders and administration site conditions:** rigors, pain, asthenia, malaise, edema
- **Respiratory, thoracic, and mediastinal disorders:** asthma, painful respiration, throat tightness
- **Skin and subcutaneous tissue disorders:** hyperhidrosis, urticaria, rash
- **Psychiatric disorders:** nervousness
- **Vascular disorders:** flushing, palpitations
- **Metabolism and nutrition disorders:** decreased appetite
- **Ear and labyrinth disorders:** vertigo

Overdosage:

There have been two confirmed reports of overdosage with AMITIZA™. The first report involved a 3-year-old child who accidentally ingested 7 to 8 capsules of 24 mcg of AMITIZA™ and fully recovered. The second report was a study subject who self-administered a total of 96 mcg AMITIZA™ per day for 8 days. The subject experienced no adverse events during this time. Additionally, in a definitive Phase 1 cardiac repolarization study, 51 patients administered a single oral dose of 144 mcg of AMITIZA™, which is 6 times the normal single administration dose. Thirty-nine (39) of the 51 patients experienced an adverse event. The adverse events reported in >1% of this group included the following: nausea (45.1%), vomiting (27.5%), diarrhea (25.5%), dizziness (17.6%), loose or watery stools (13.7%), headache (11.8%), retching (7.8%), abdominal pain (5.9%), flushing or hot flush (5.9%), dyspnea (3.9%), pallor (3.9%), stomach discomfort (3.9%), syncope (3.9%), upper abdominal pain (2.0%), anorexia (2.0%), asthenia (2.0%), chest discomfort (2.0%), dry mouth (2.0%), hyperhidrosis (2.0%), skin irritation (2.0%) and vasovagal episode (2.0%).

DOSAGE AND ADMINISTRATION

The recommended dosage for AMITIZA™ is 24 mcg taken twice daily (BID) orally with food. Physicians and patients should periodically assess the need for continued therapy.

HOW SUPPLIED

AMITIZA™ is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 mcg lubiprostone. AMITIZA™ is available as follows:

Bottles of 100.....NDC 64764-240-10

STORAGE

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

MARKETED BY:

Sucampo Pharmaceuticals, Inc.
Bethesda, MD 20814

and

Takeda Pharmaceuticals America, Inc.
Lincolnshire, IL 60069

PRODUCT OF THE UNITED STATES

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Julie Beitz
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EXHIBIT 4

US005284858A

United States Patent [19]

Ueno et al.

[11] Patent Number: 5,284,858

[45] Date of Patent: Feb. 8, 1994

[54] PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME

[75] Inventors: **Ryuzo Ueno**, Nishinomiya; **Ryuji Ueno**, Kyoto; **Ichie Kato**, Kawanishi; **Tomio Oda**, Itami, all of Japan

[73] Assignee: **Kabushiki Kaisha Ueno Seiyaku Oyo Kenkyujo**, Osaka, Japan

[21] Appl. No.: **925,220**

[22] Filed: **Aug. 6, 1992**

Related U.S. Application Data

[60] Division of Ser. No. 700,895, May 13, 1991, Pat. No. 5,166,174, which is a continuation of Ser. No. 406,830, Sep. 12, 1989, abandoned, which is a continuation-in-part of Ser. No. 149,445, Jan. 28, 1988, abandoned.

[30] **Foreign Application Priority Data**

Jan. 28, 1987 [JP] Japan 62-18820
Mar. 18, 1987 [JP] Japan 62-65352

[51] **Int. Cl.**[5] **C07G 405/00**; A61K 31/557
[52] **U.S. Cl.** **514/530**; 514/573; 560/121; 562/503
[58] **Field of Search** 514/530, 573; 560/121; 562/503

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European Search Report EP 88 30 0709.

Primary Examiner—Robert Gerstl
Attorney, Agent, or Firm—Sughrue, Mion, Zinn, Macpeak & Seas

[57] **ABSTRACT**

The novel 13, 14-dihydro-15-keto prostaglandins E of the invention have remarkable preventive effects against ulcers. Further, the novel 13,14-dihydro-15-ketoprostaglandins E of the invention have an advatage that they have none of side effects which prostaglandin E intrinsically has, or can remarakably reduce such effects of the prostaglandin E.

Therefore, the novel 13, 14-dihydro-15-keto prostaglandins E of the invention are effective for animal and human use for treatment and prevention of ulcers, such as duodenal ulcer and gastric ulcer.

13 Claims, 57 Drawing Sheets

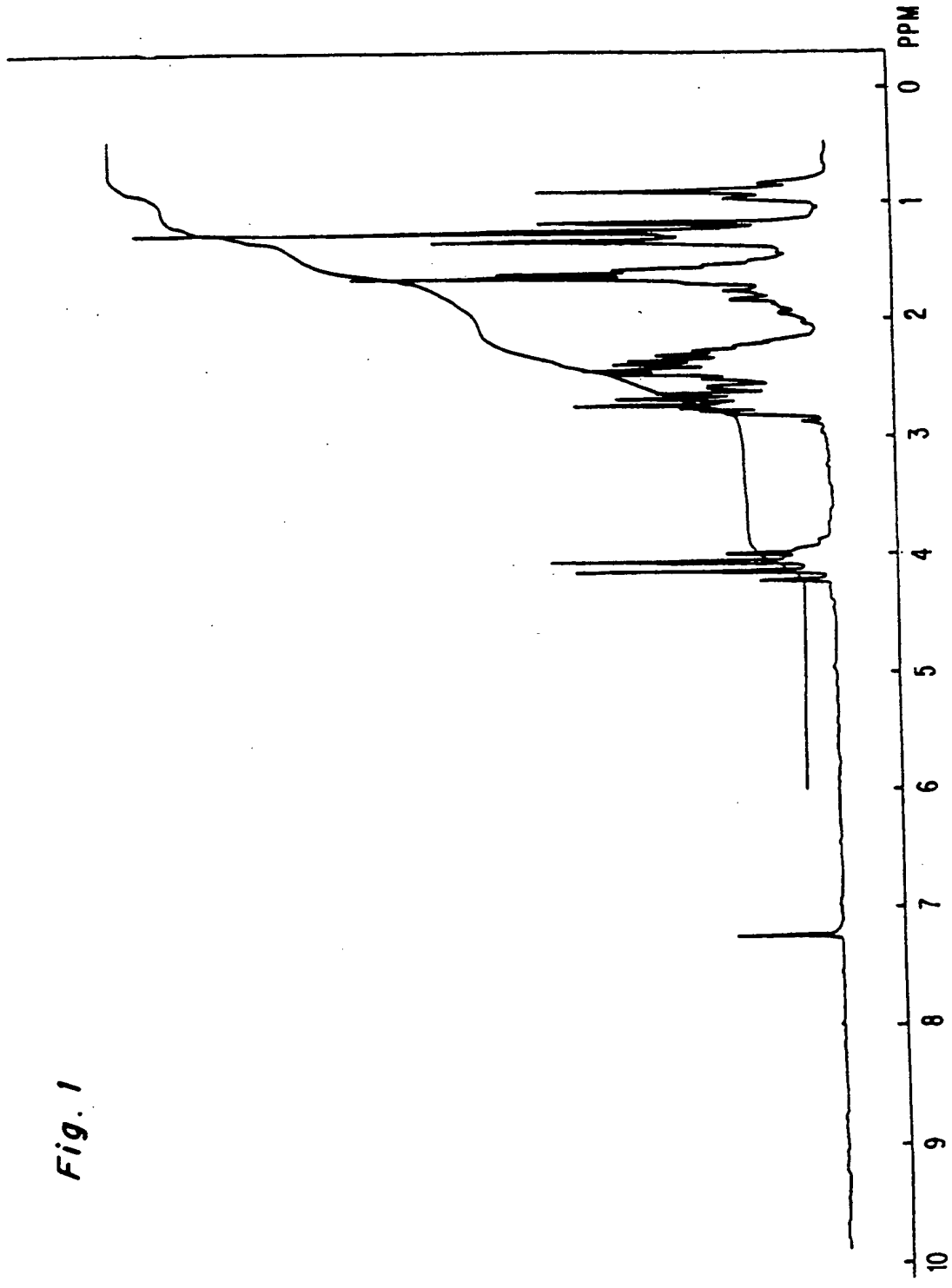


Fig. 1

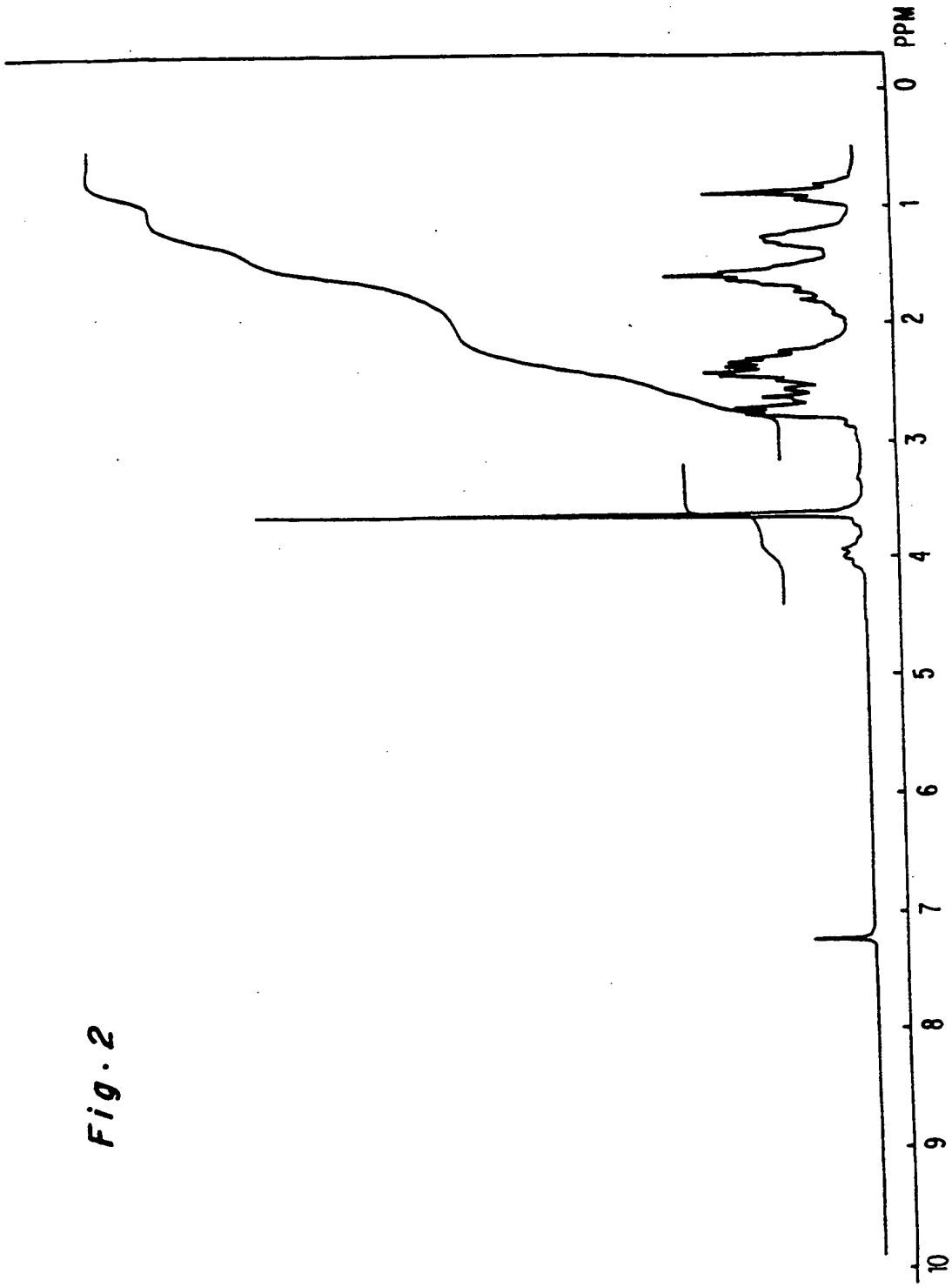


Fig. 2

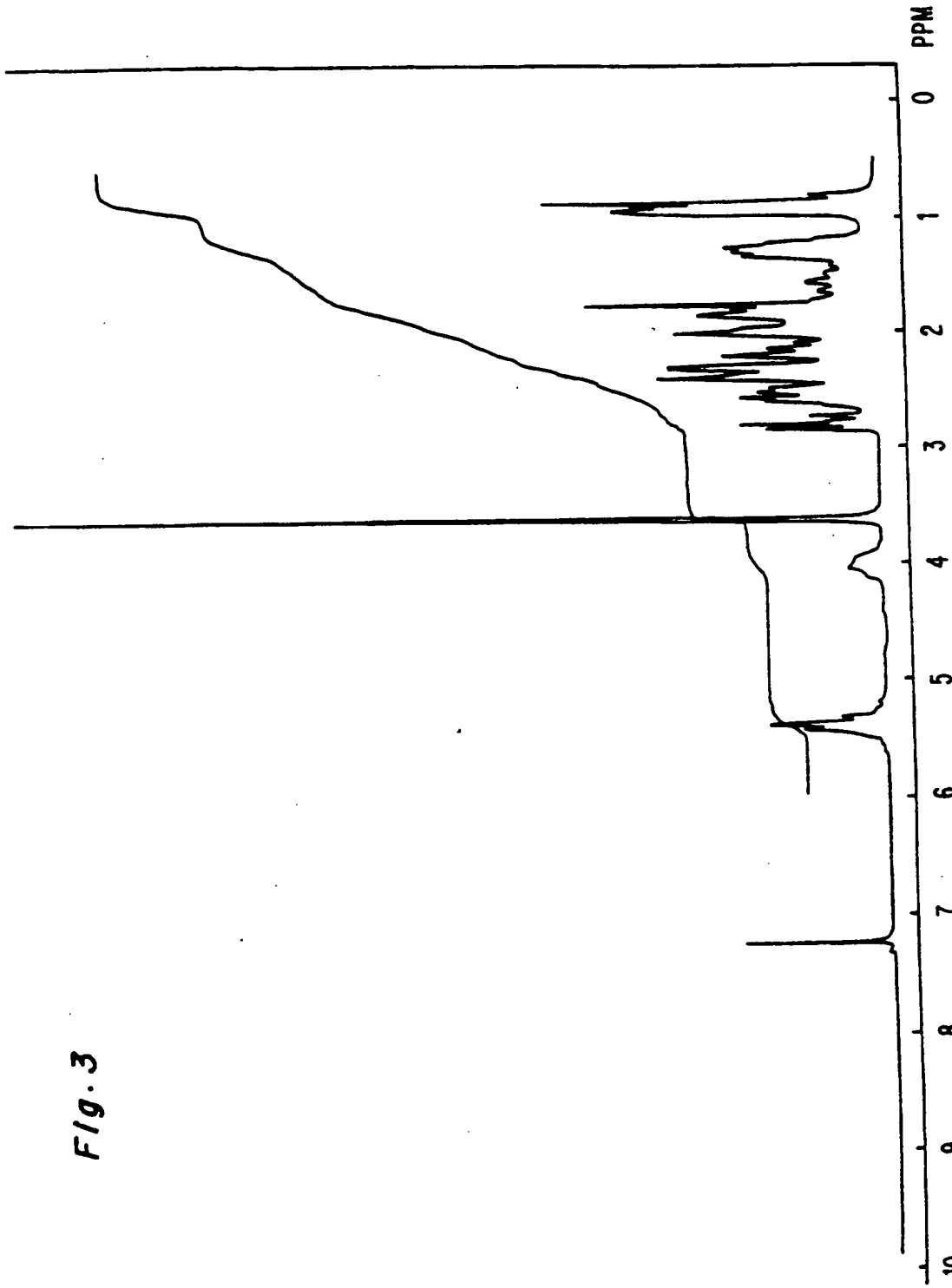


Fig. 3

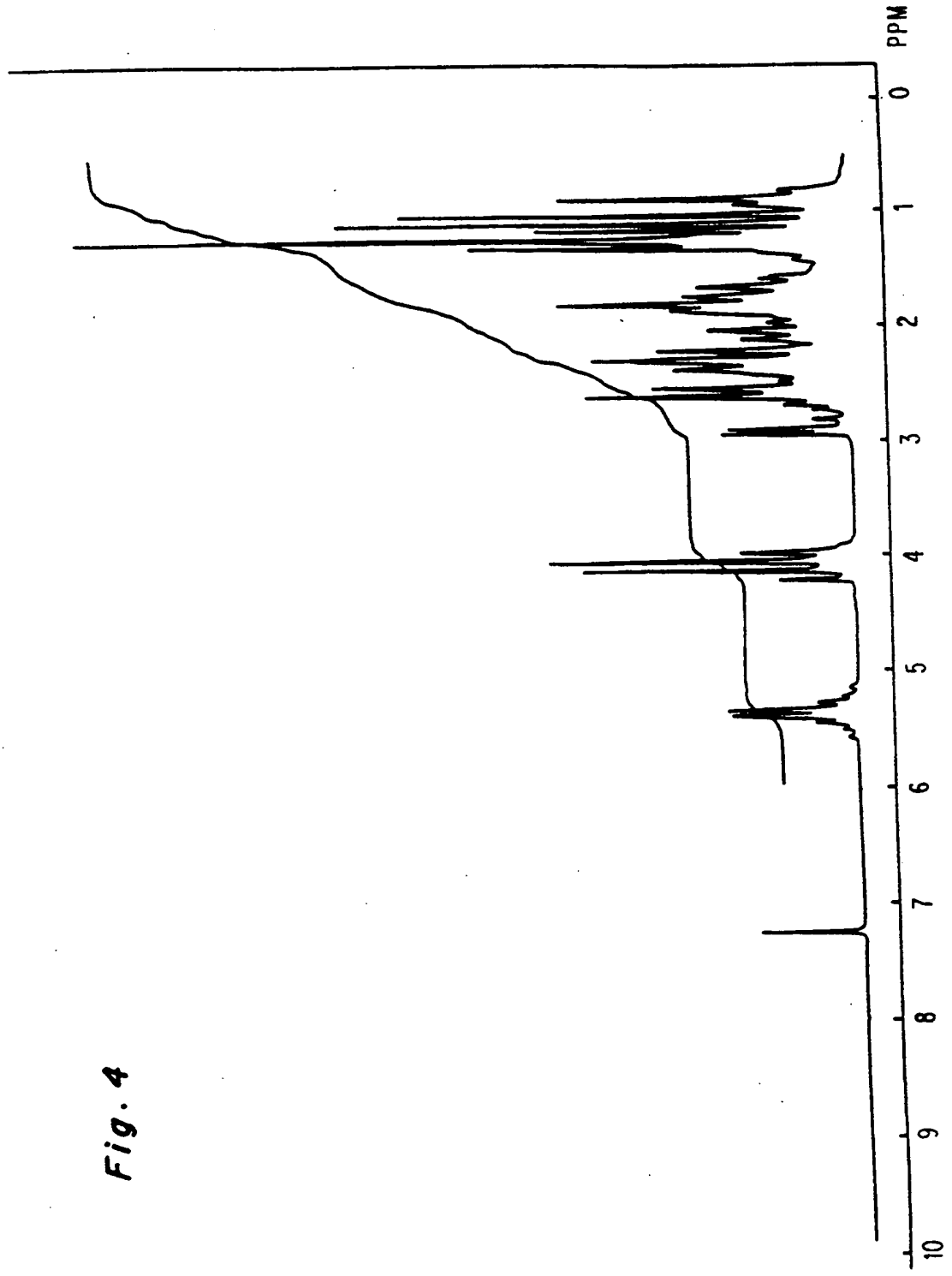


Fig. 4

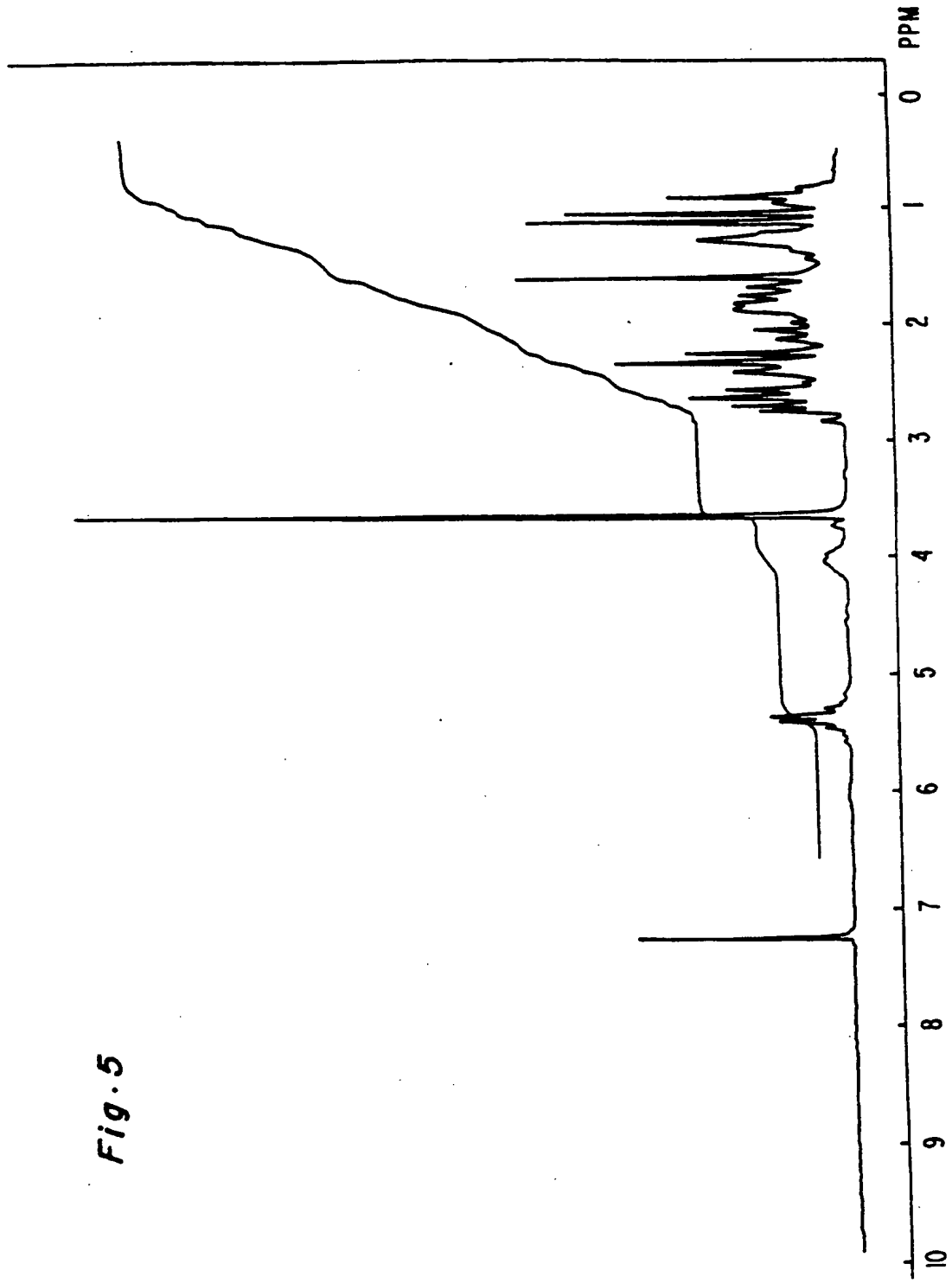


Fig. 5

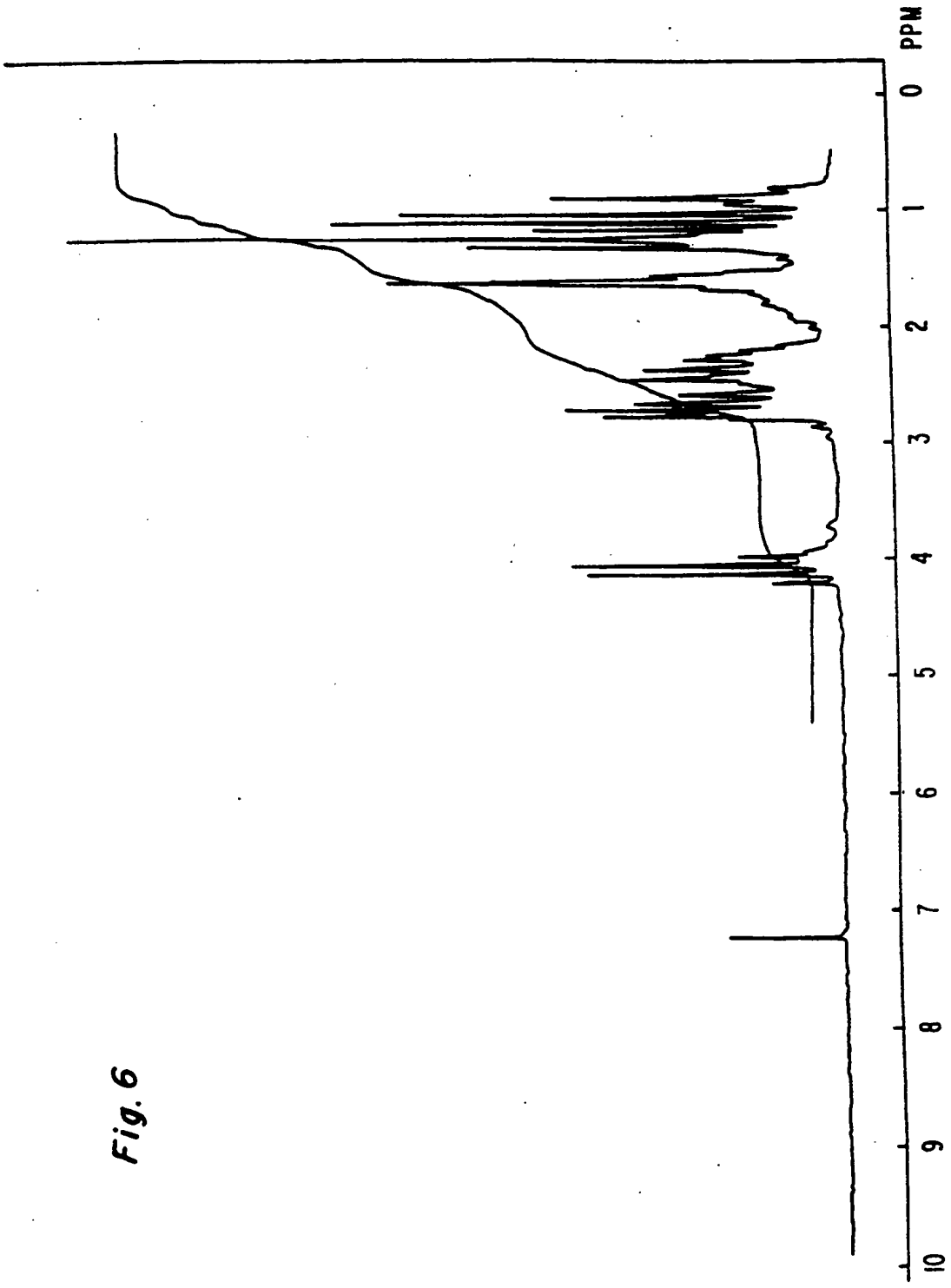


Fig. 6

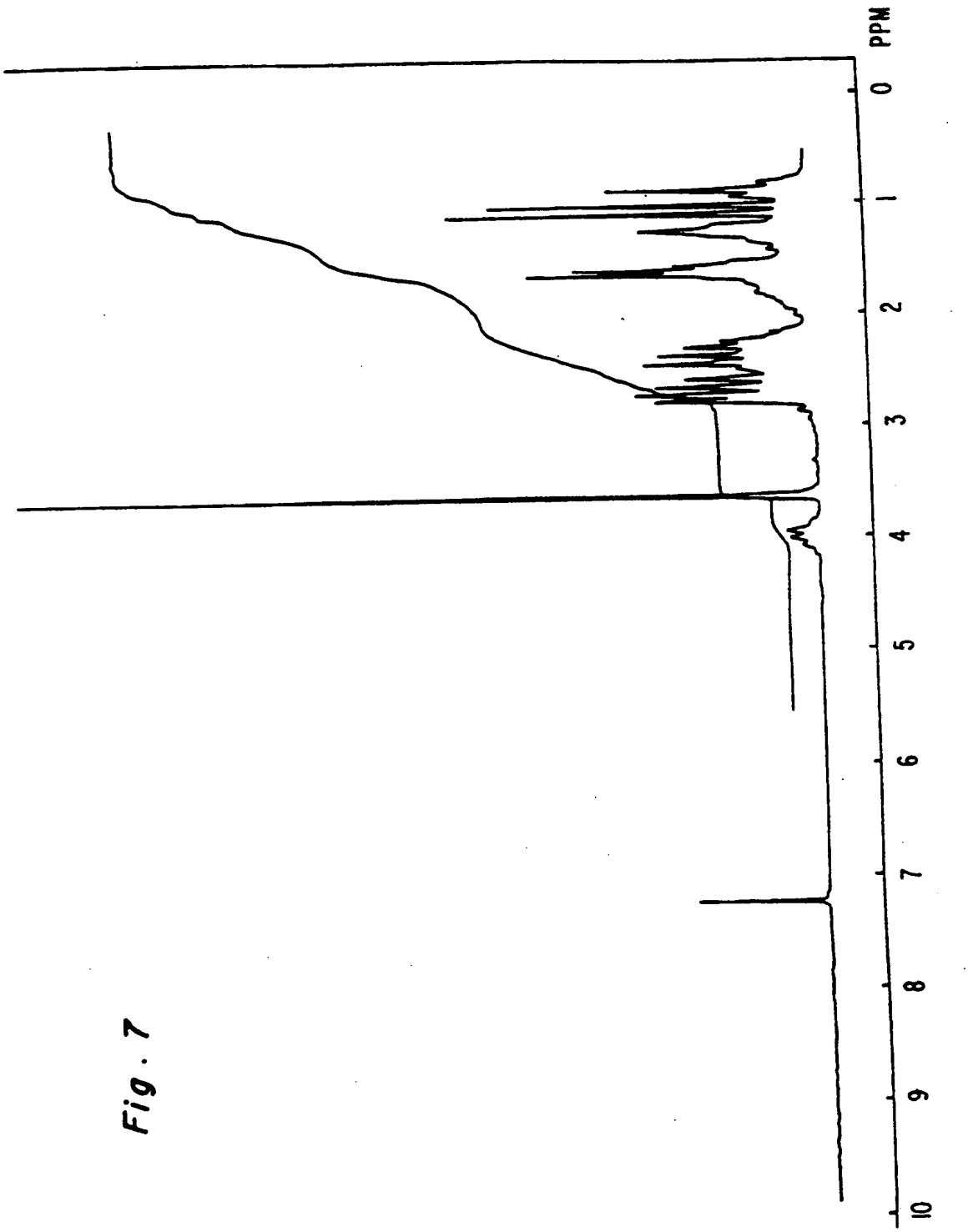


Fig. 7

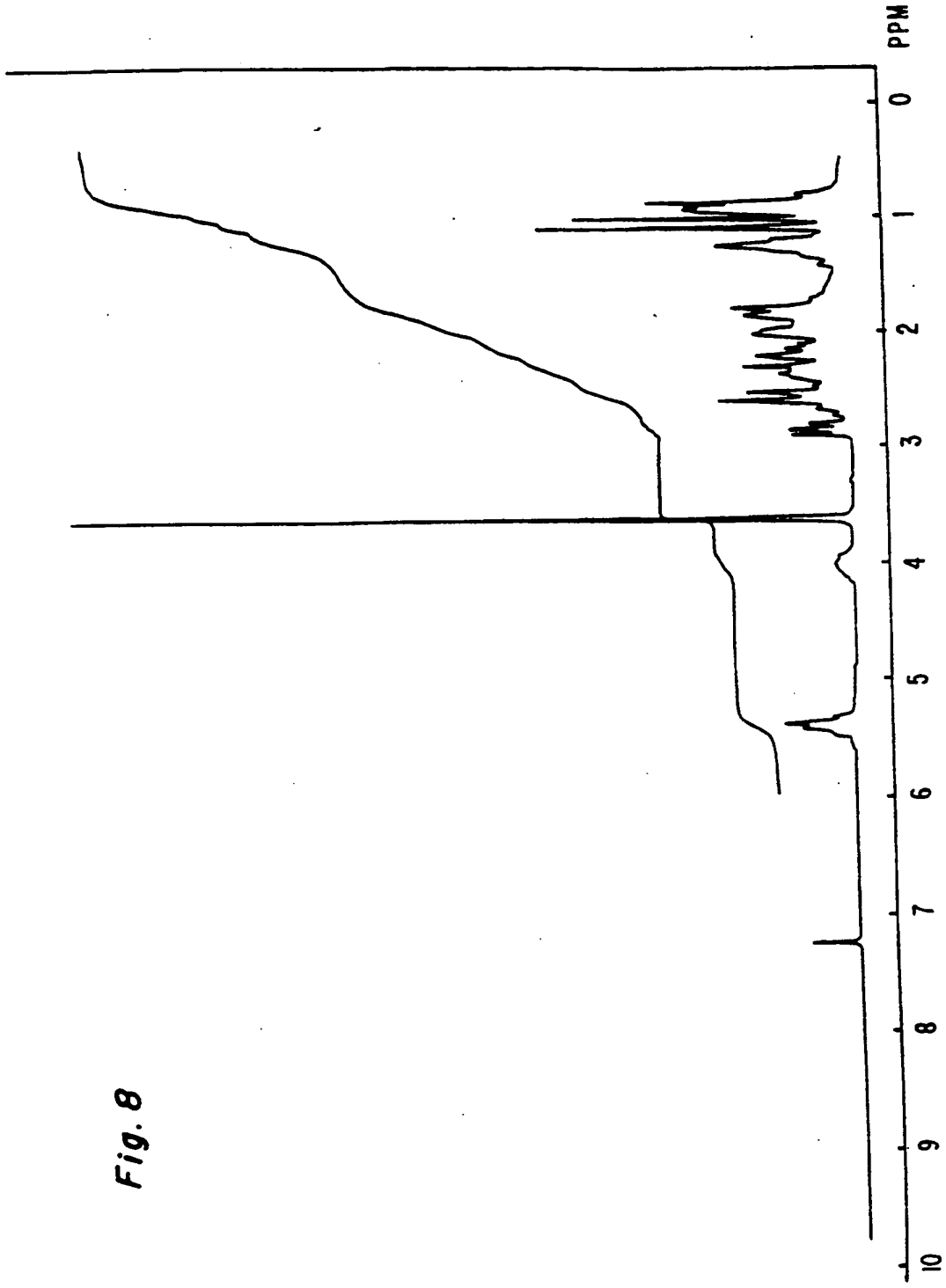
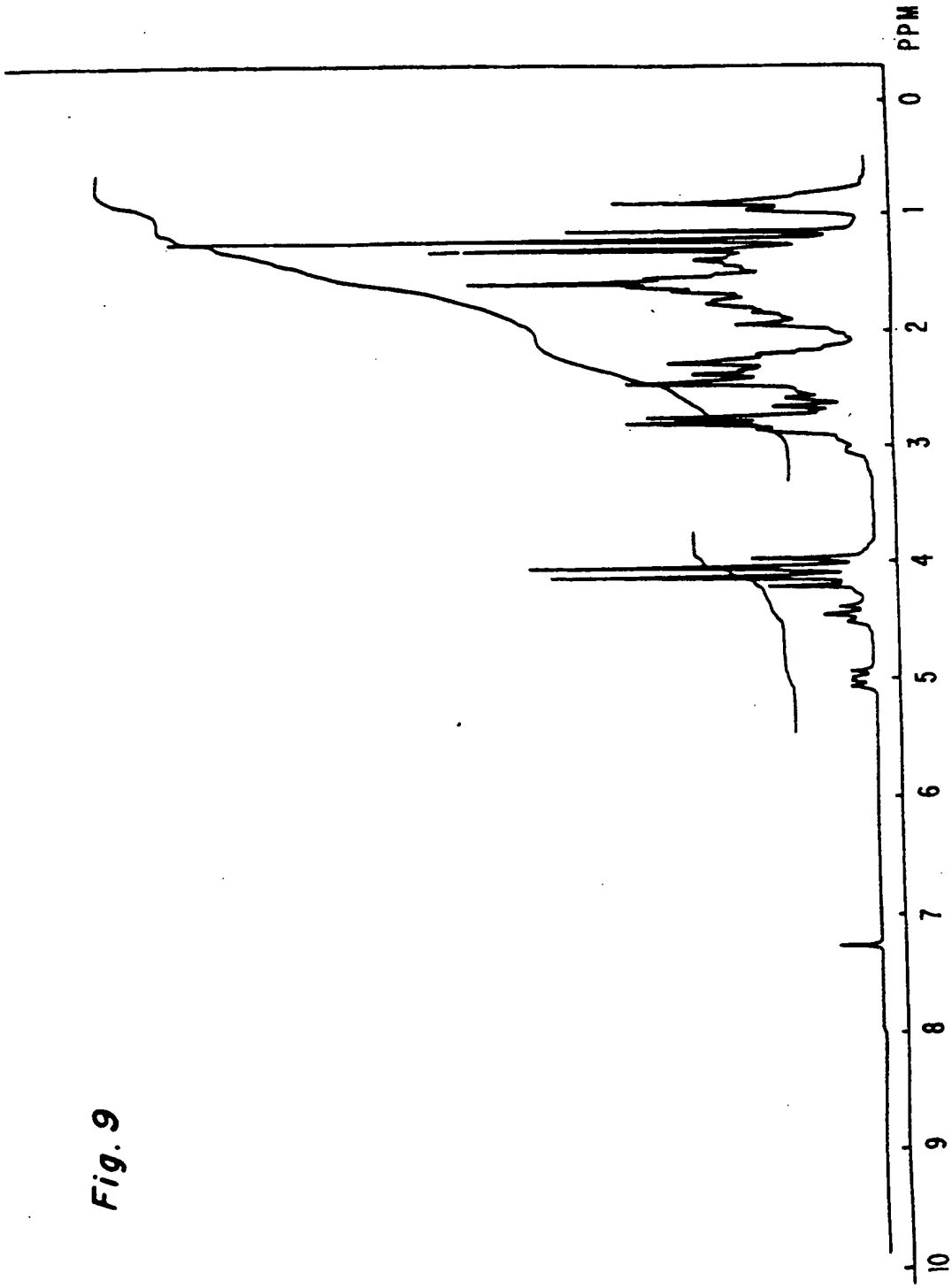


Fig. 8



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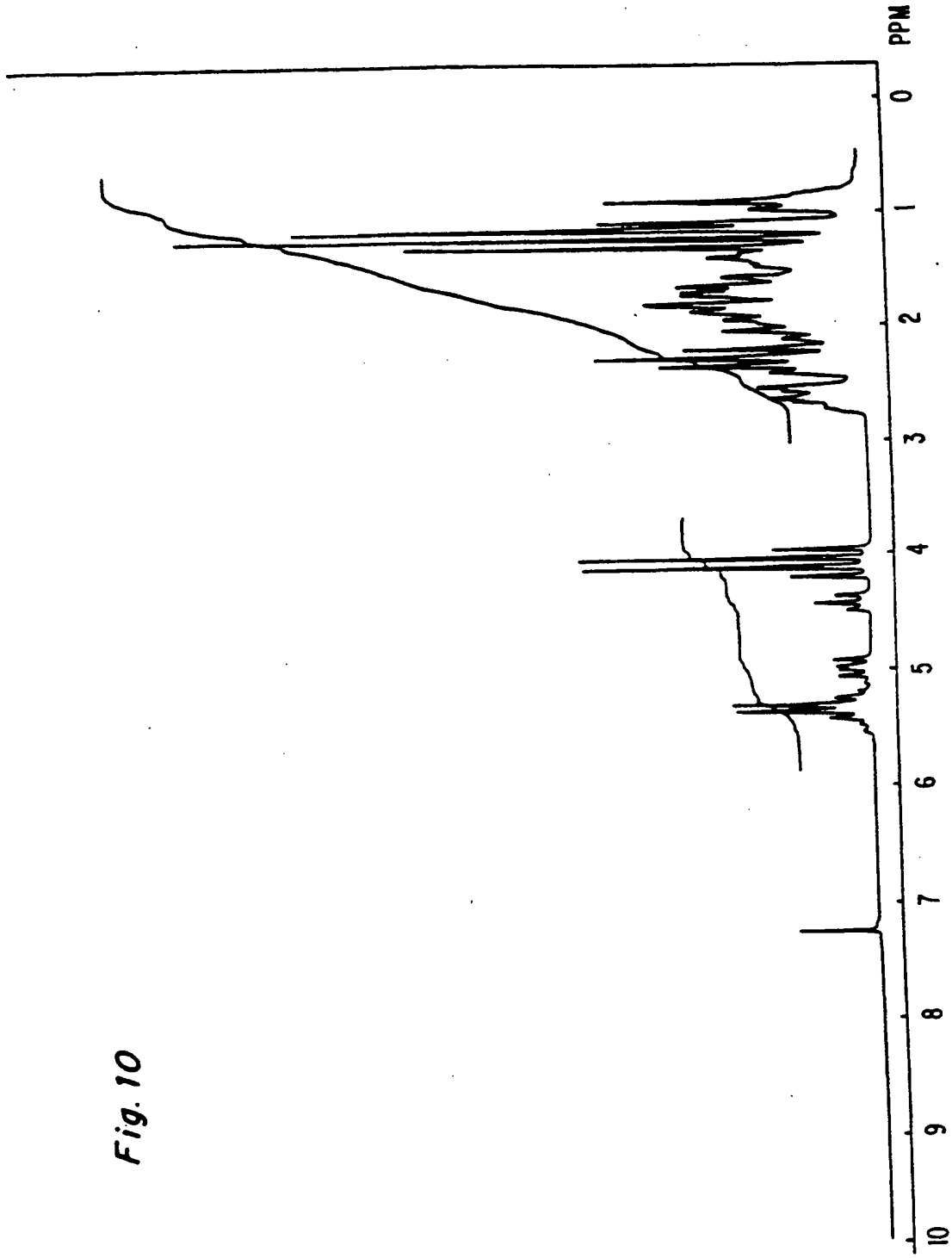


Fig. 10

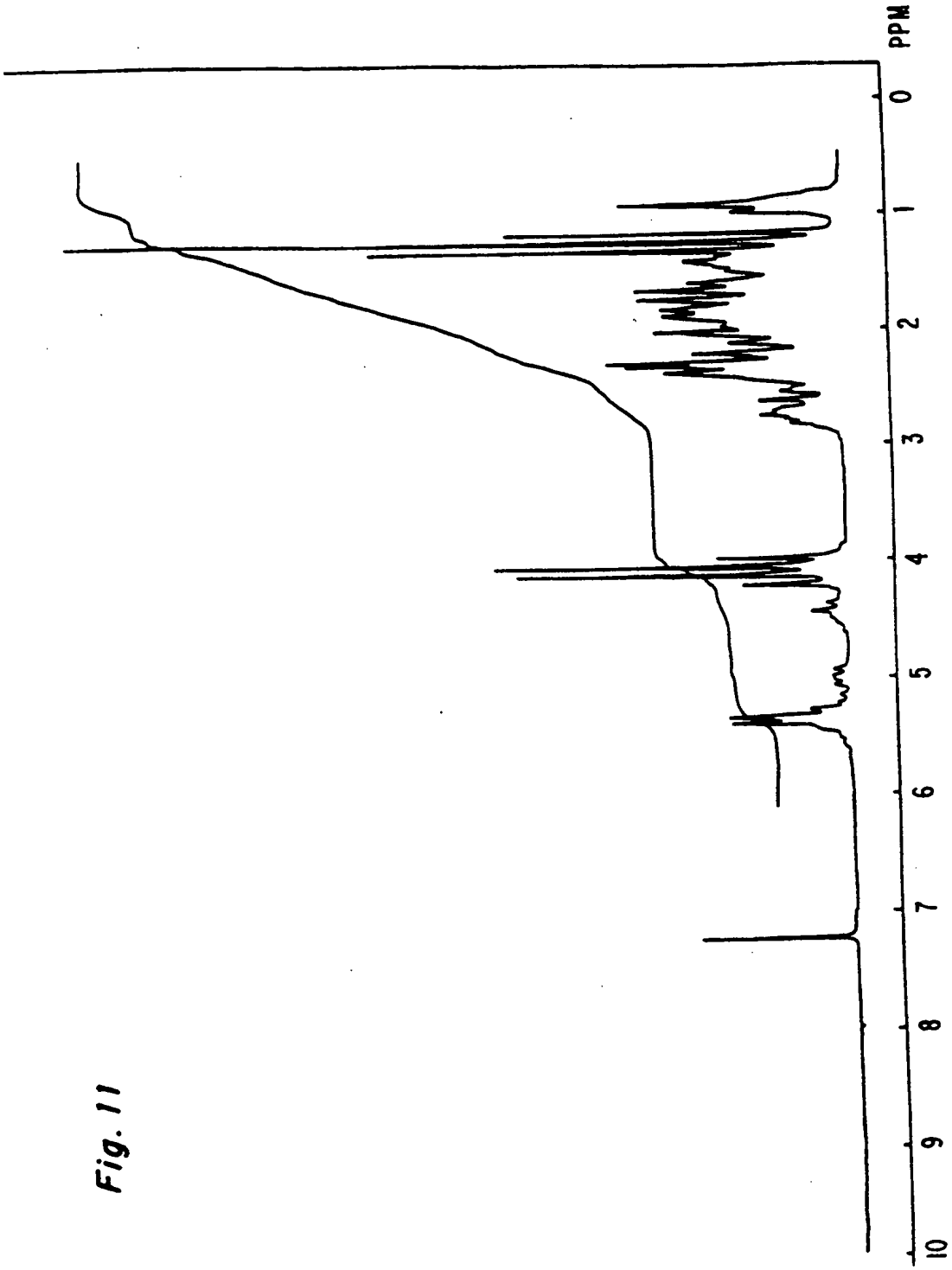
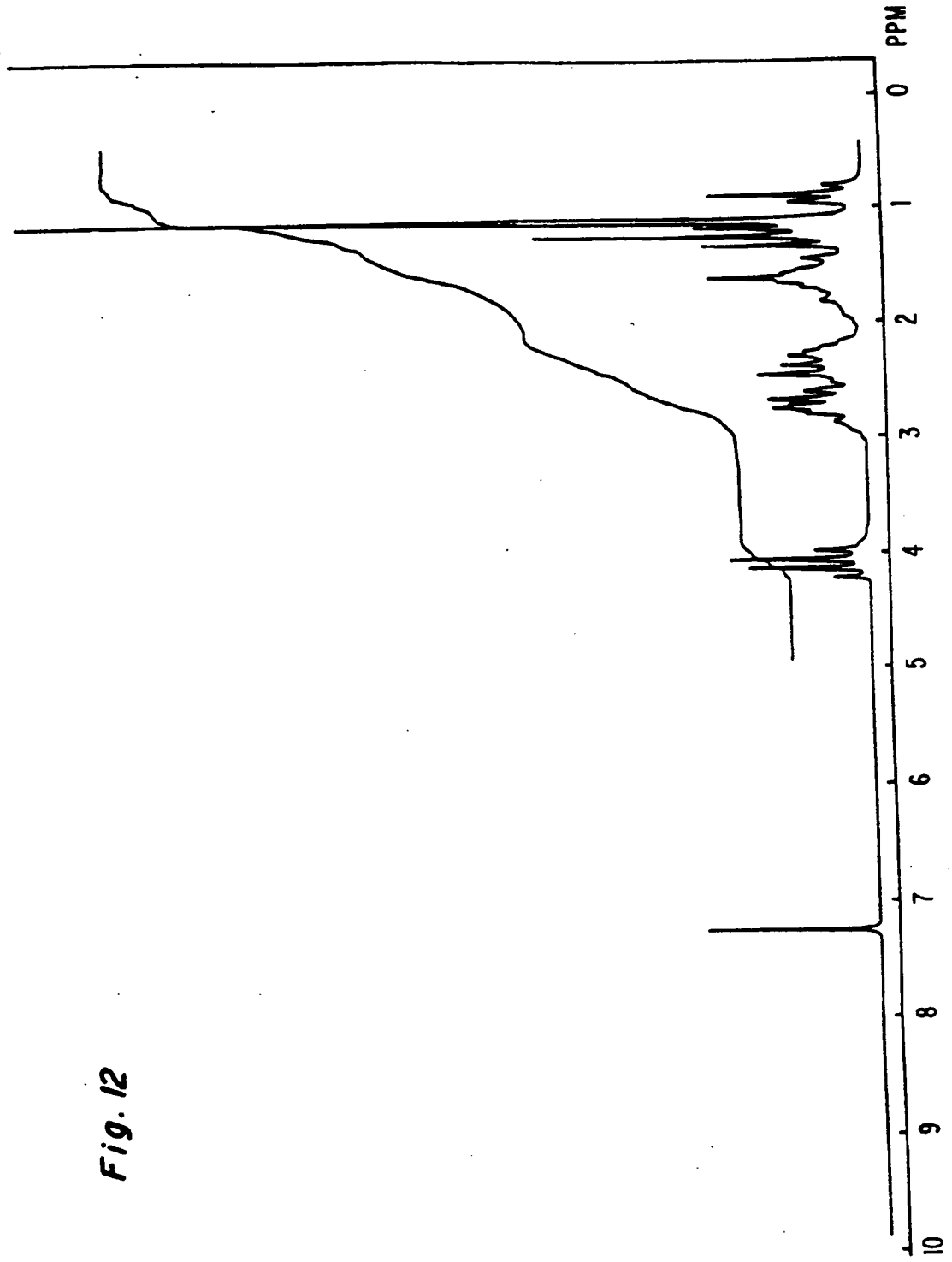


Fig. 11



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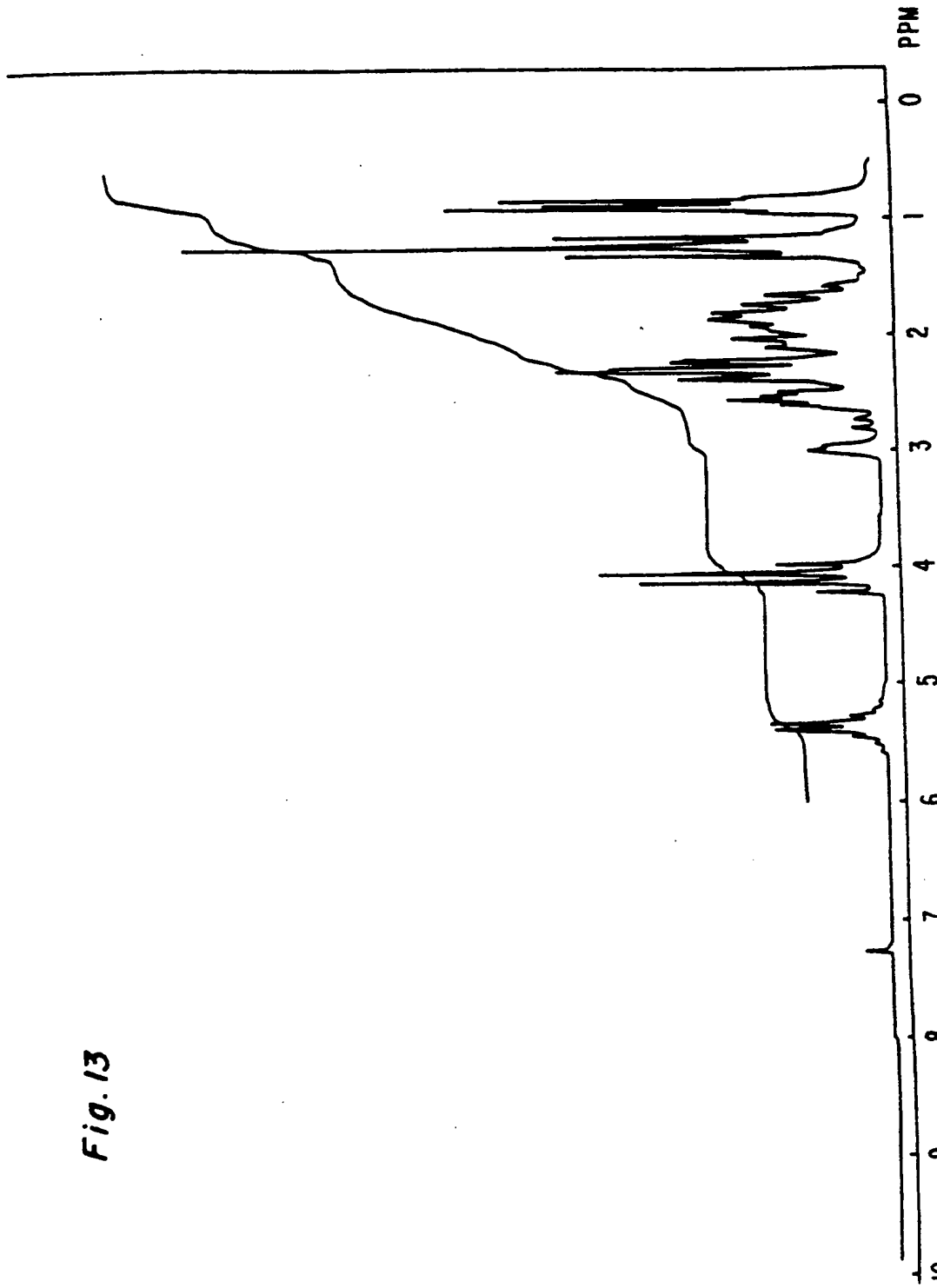

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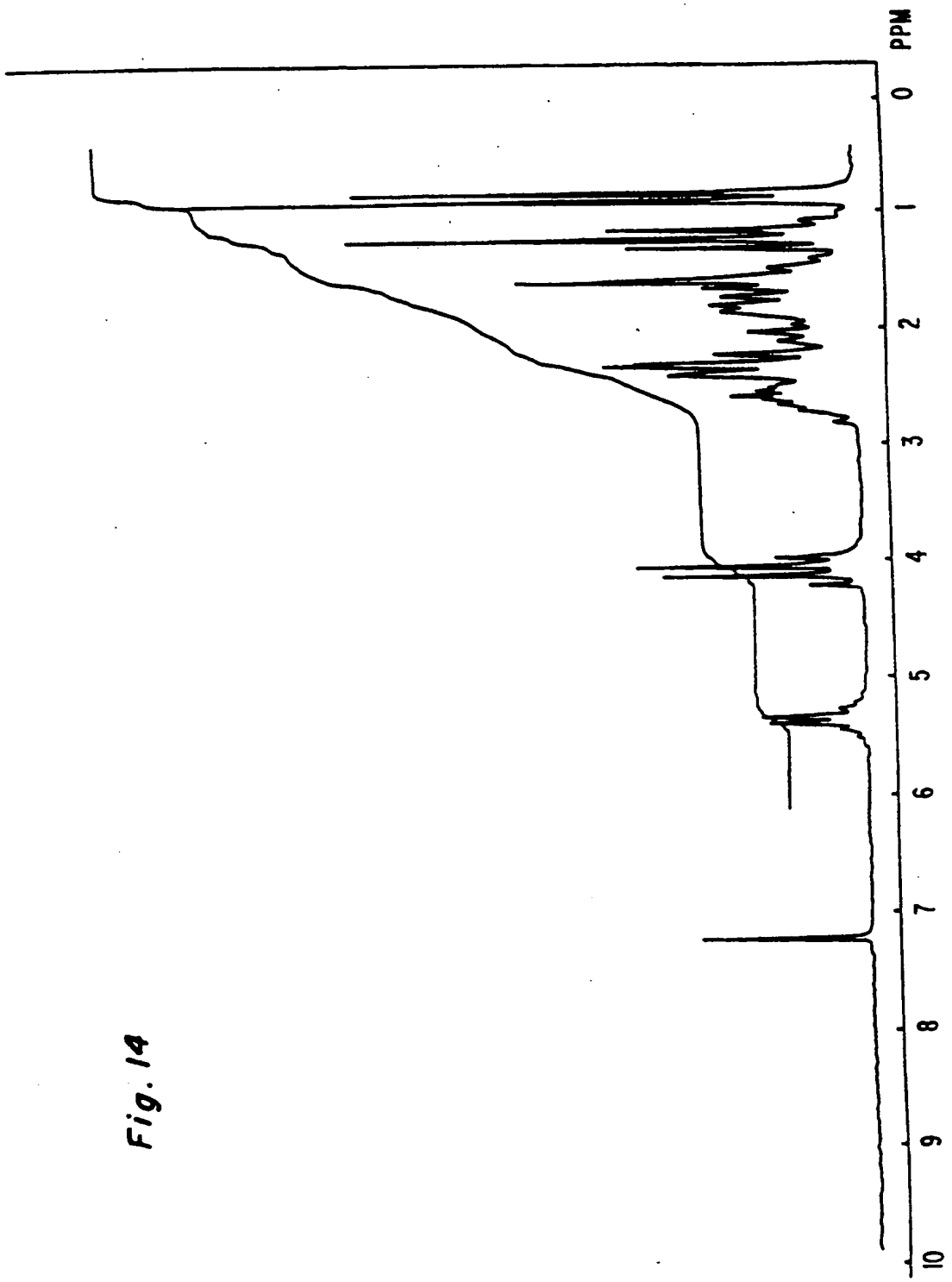

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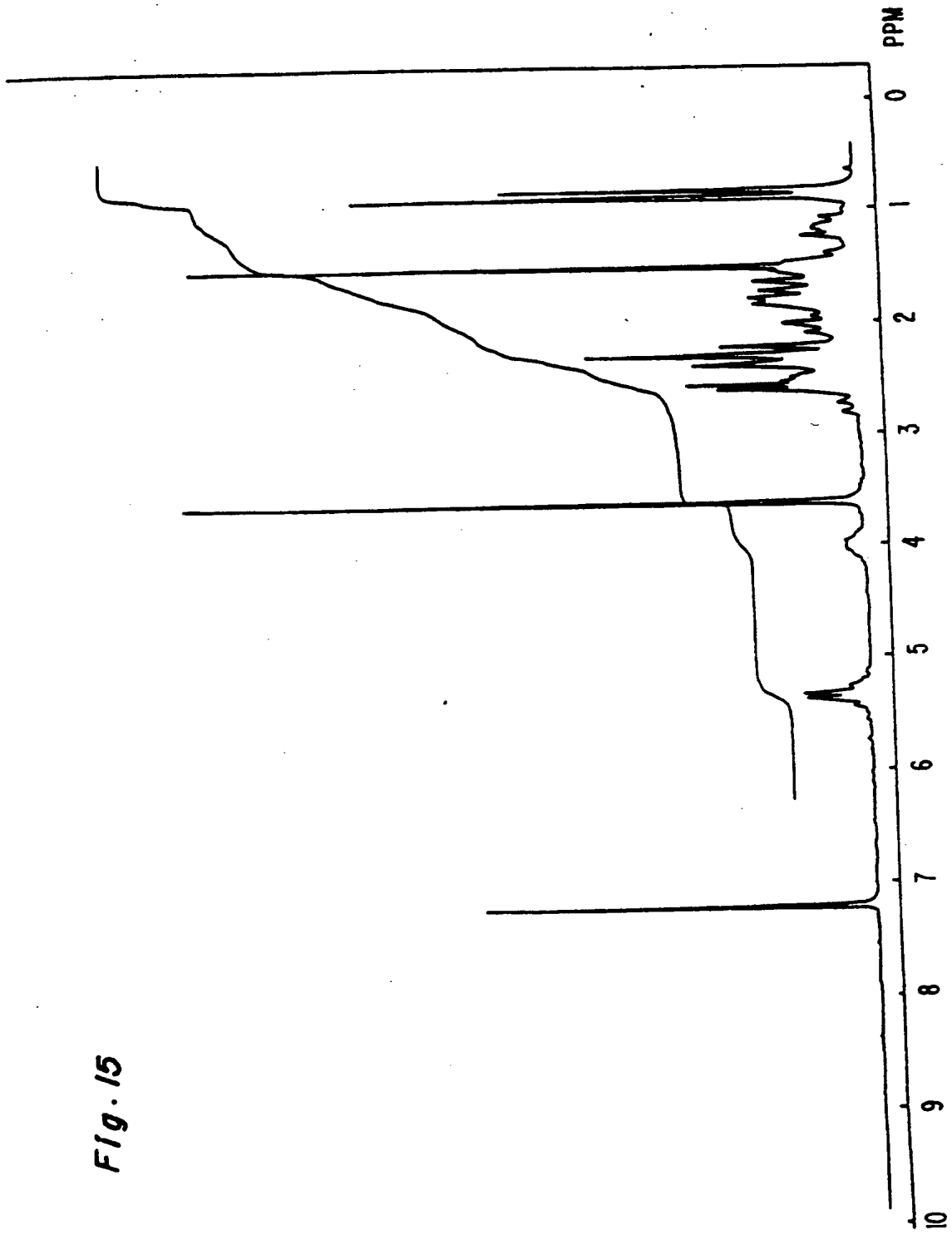

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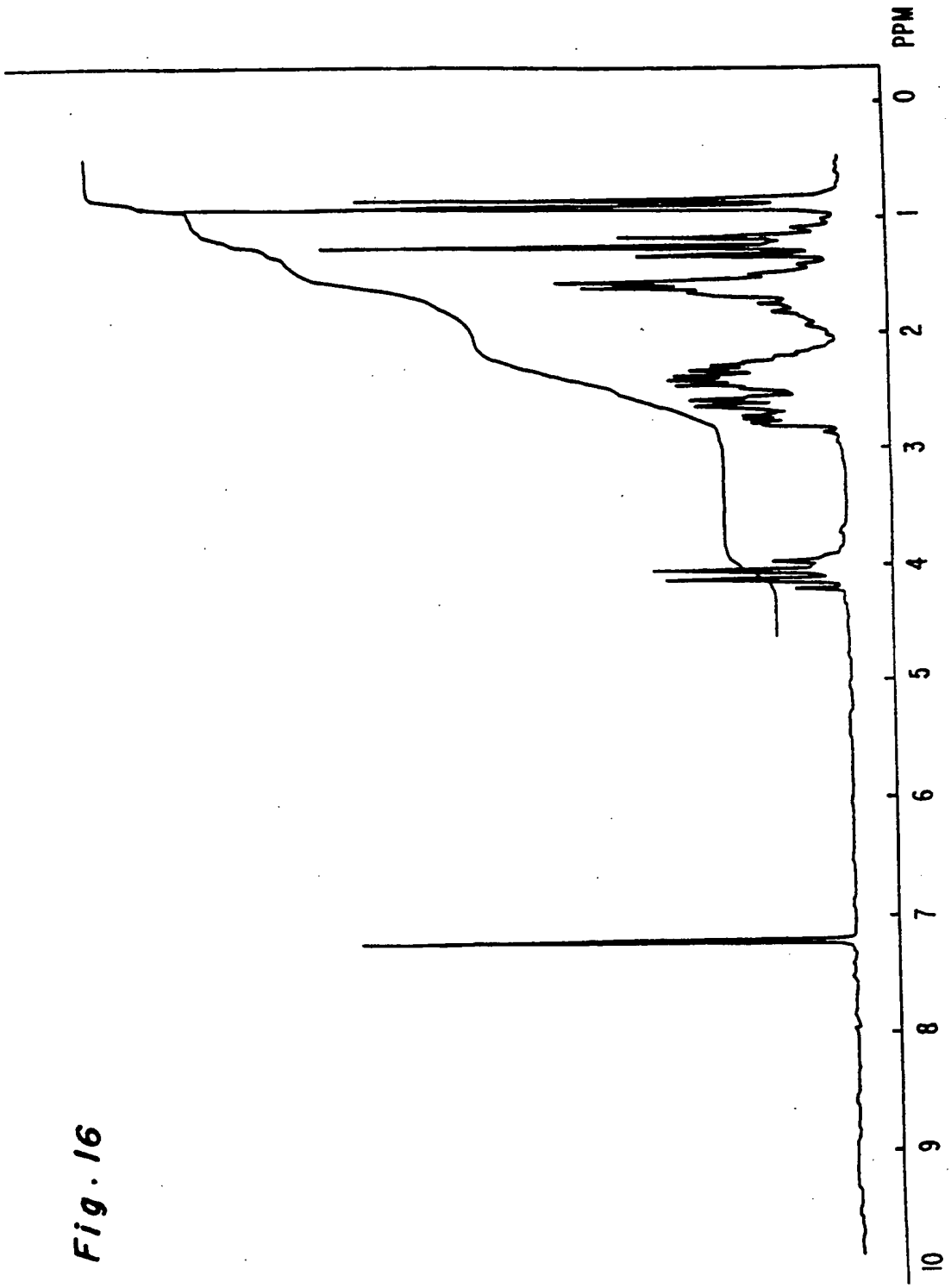

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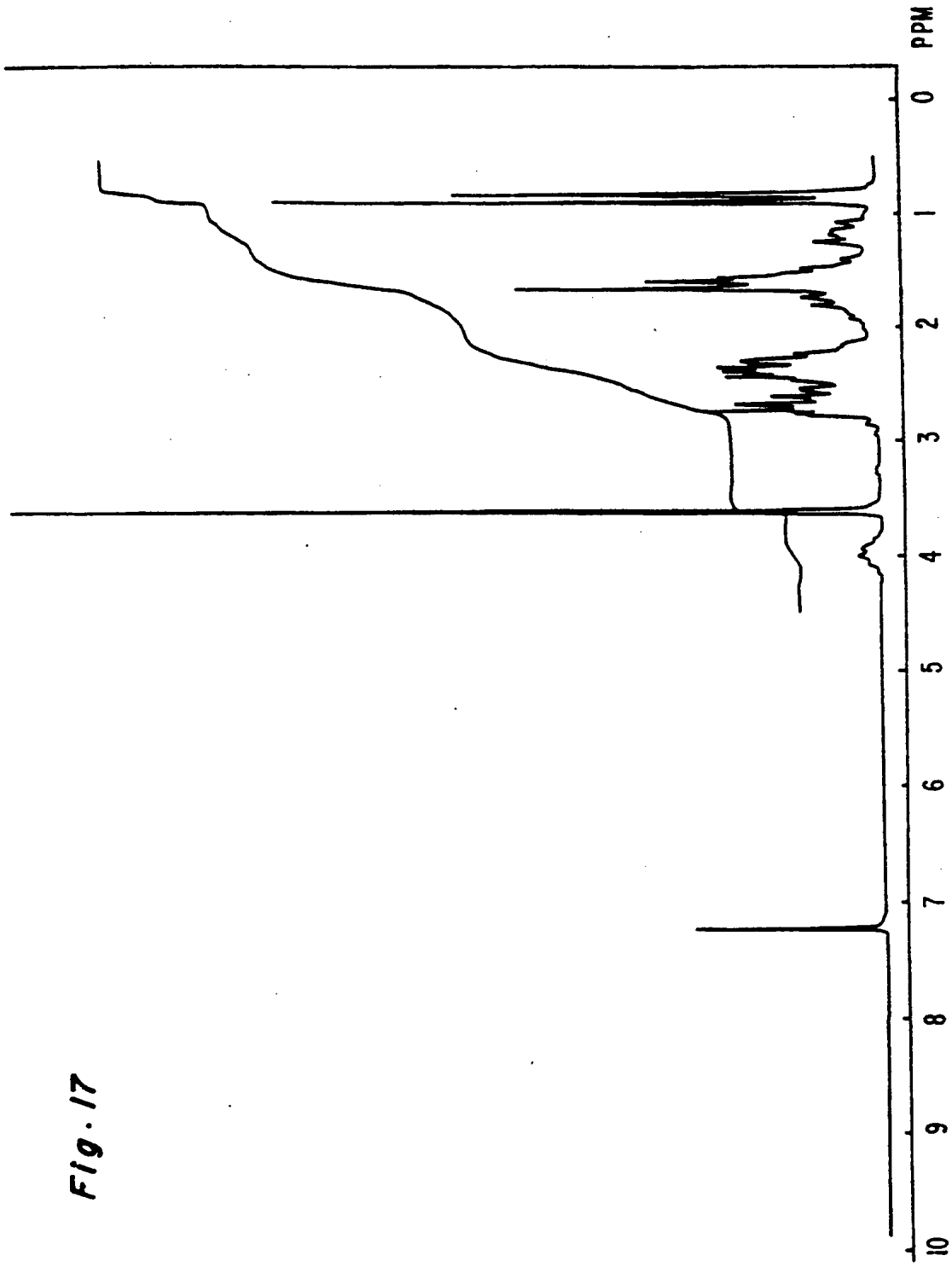

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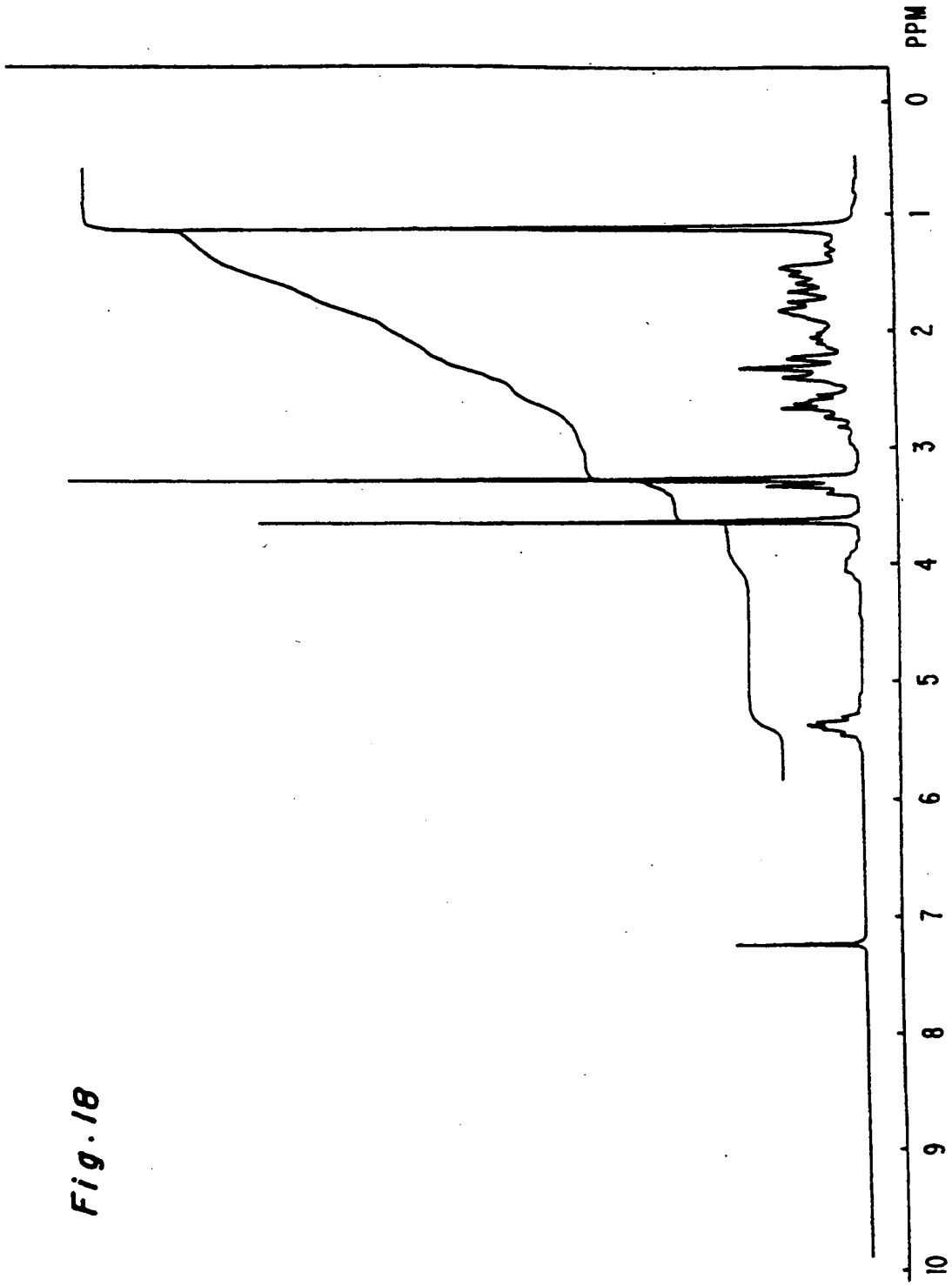

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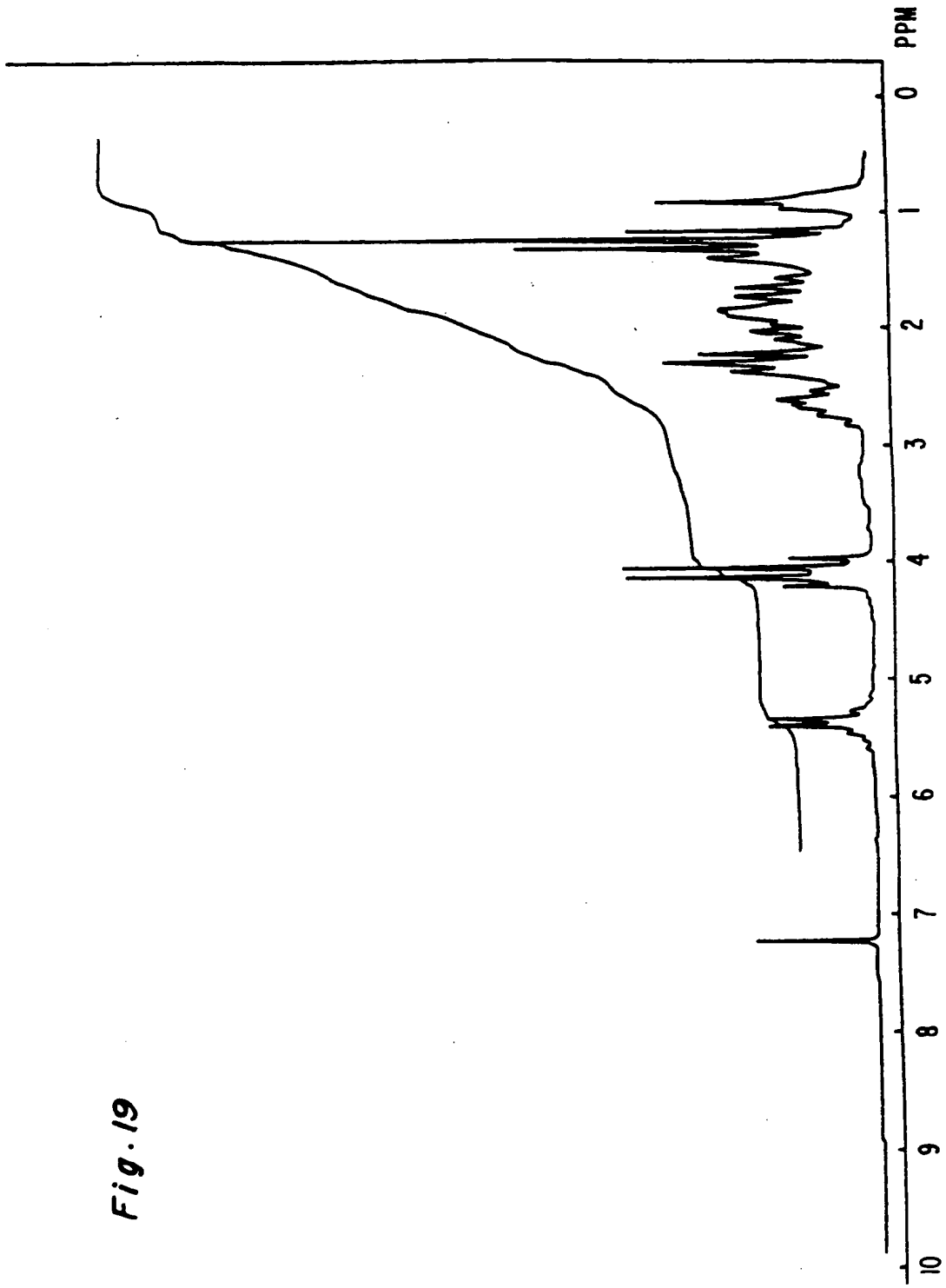
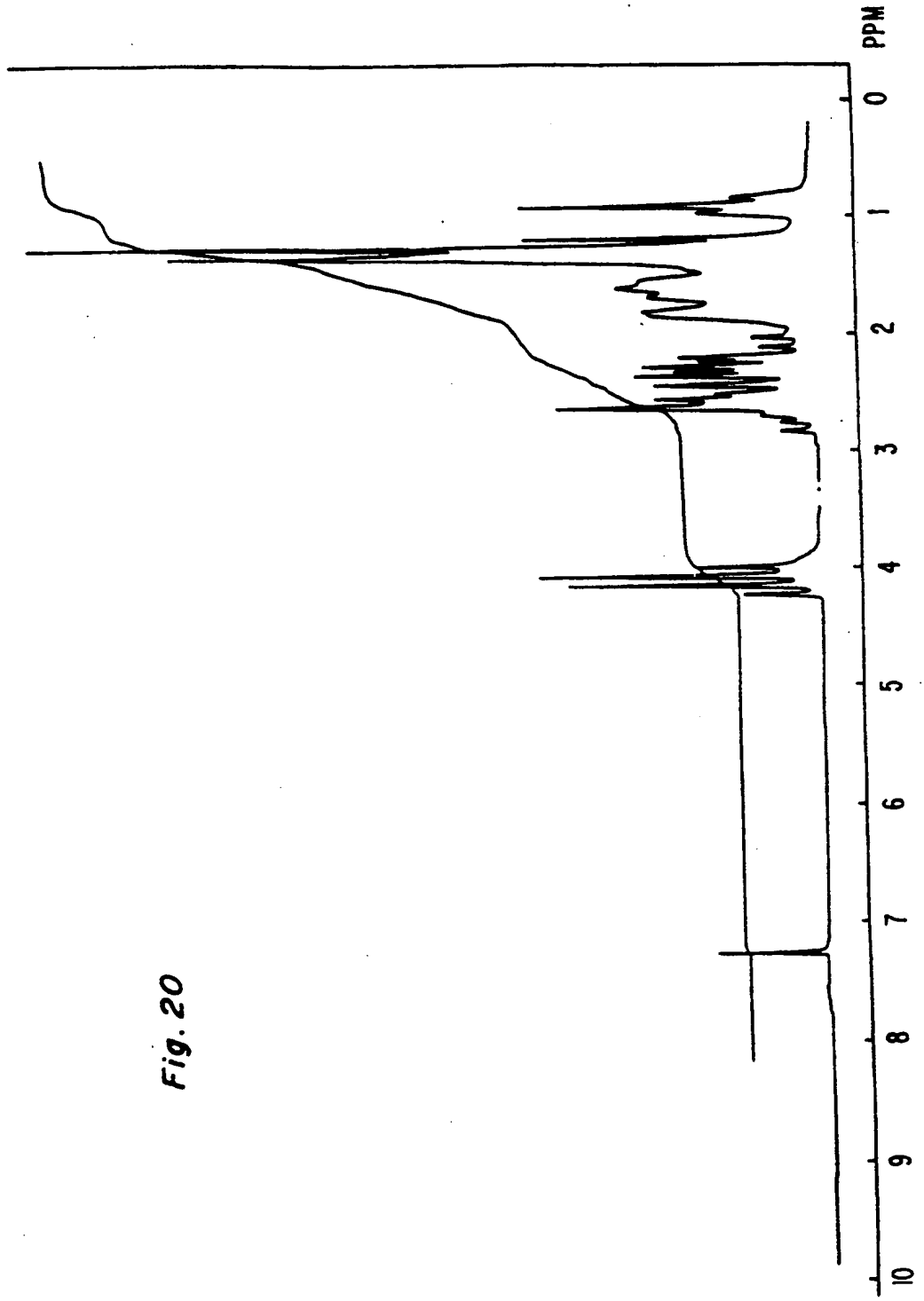


Fig. 19



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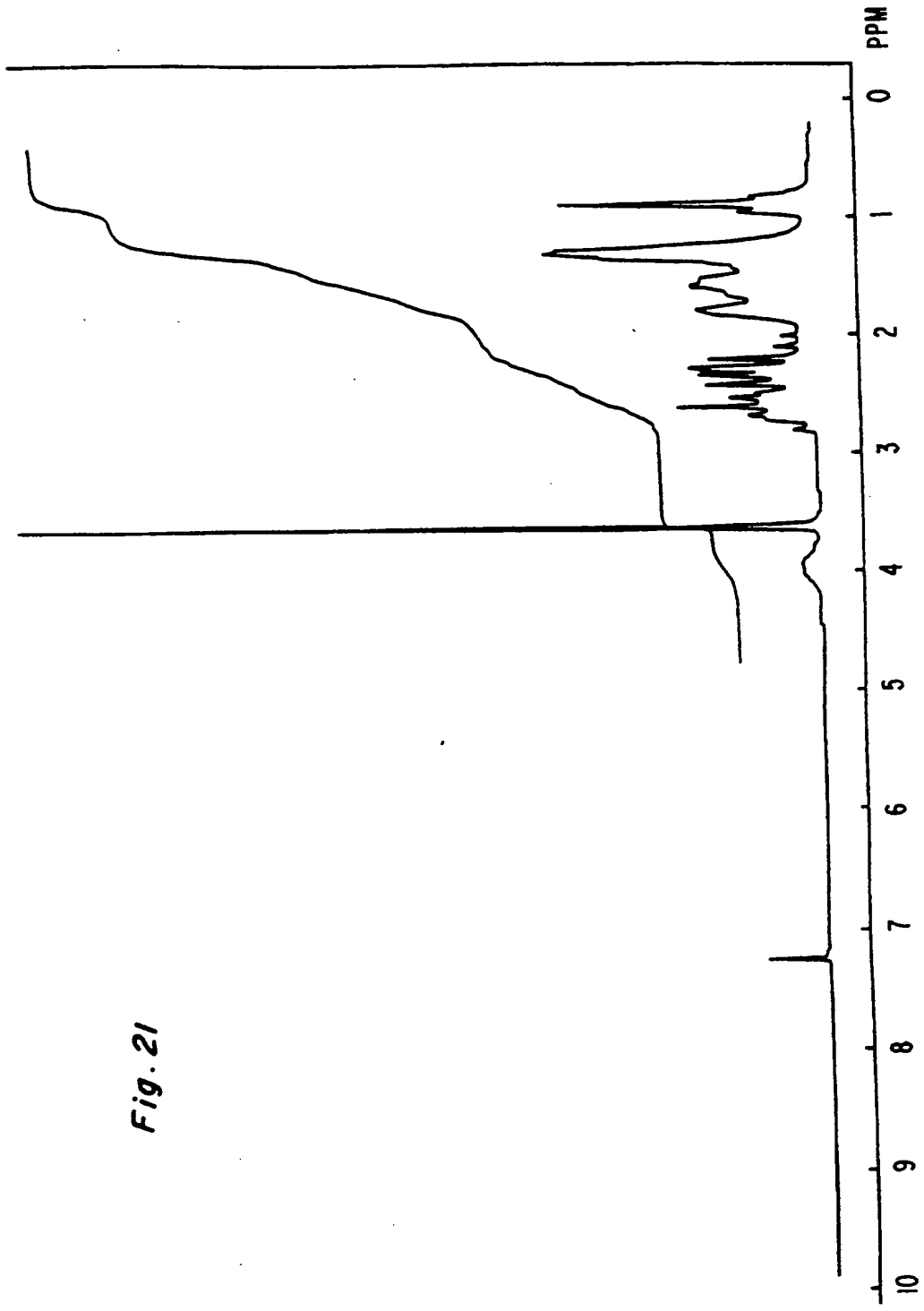
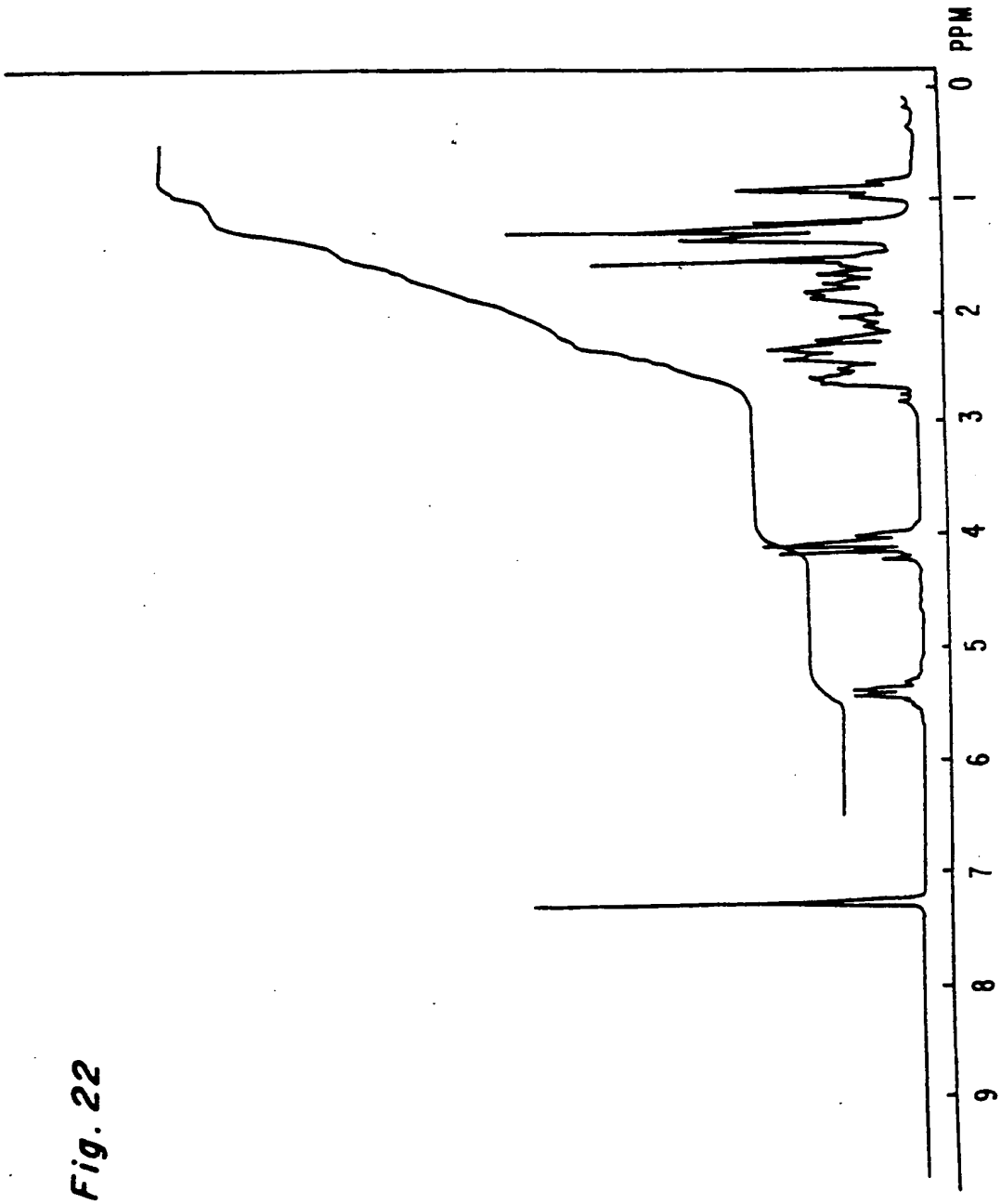


Fig. 21



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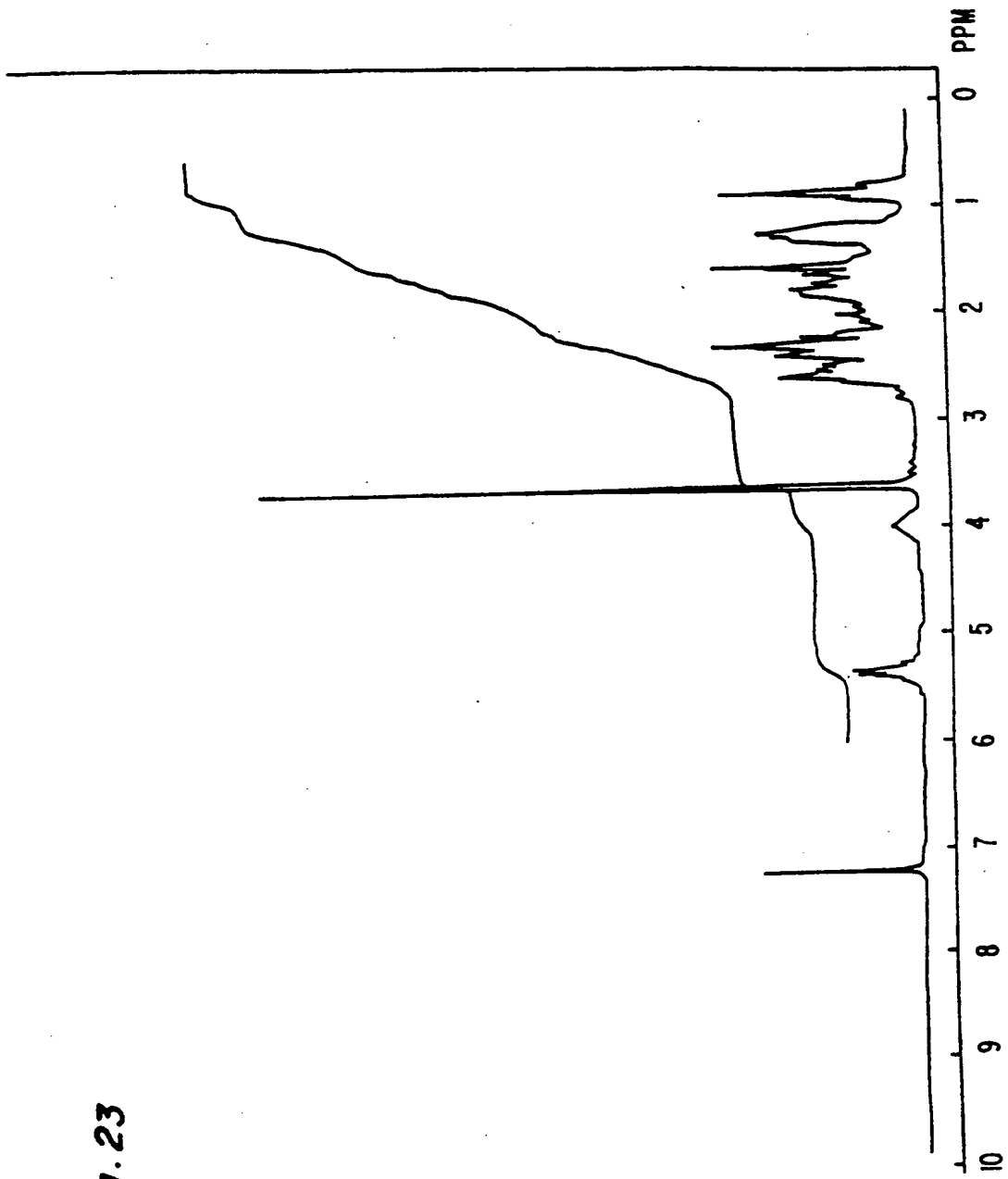


Fig. 23

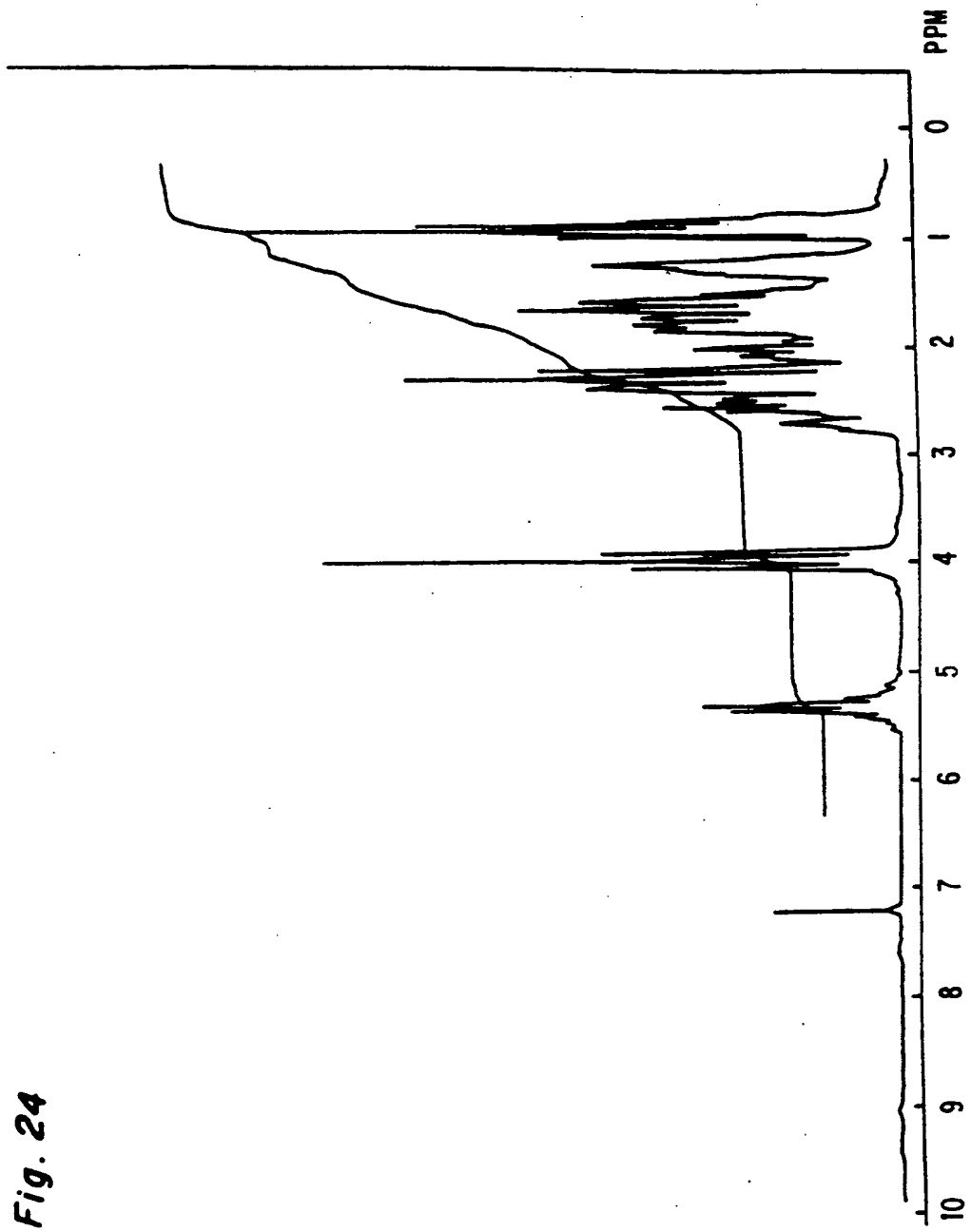


Fig. 24

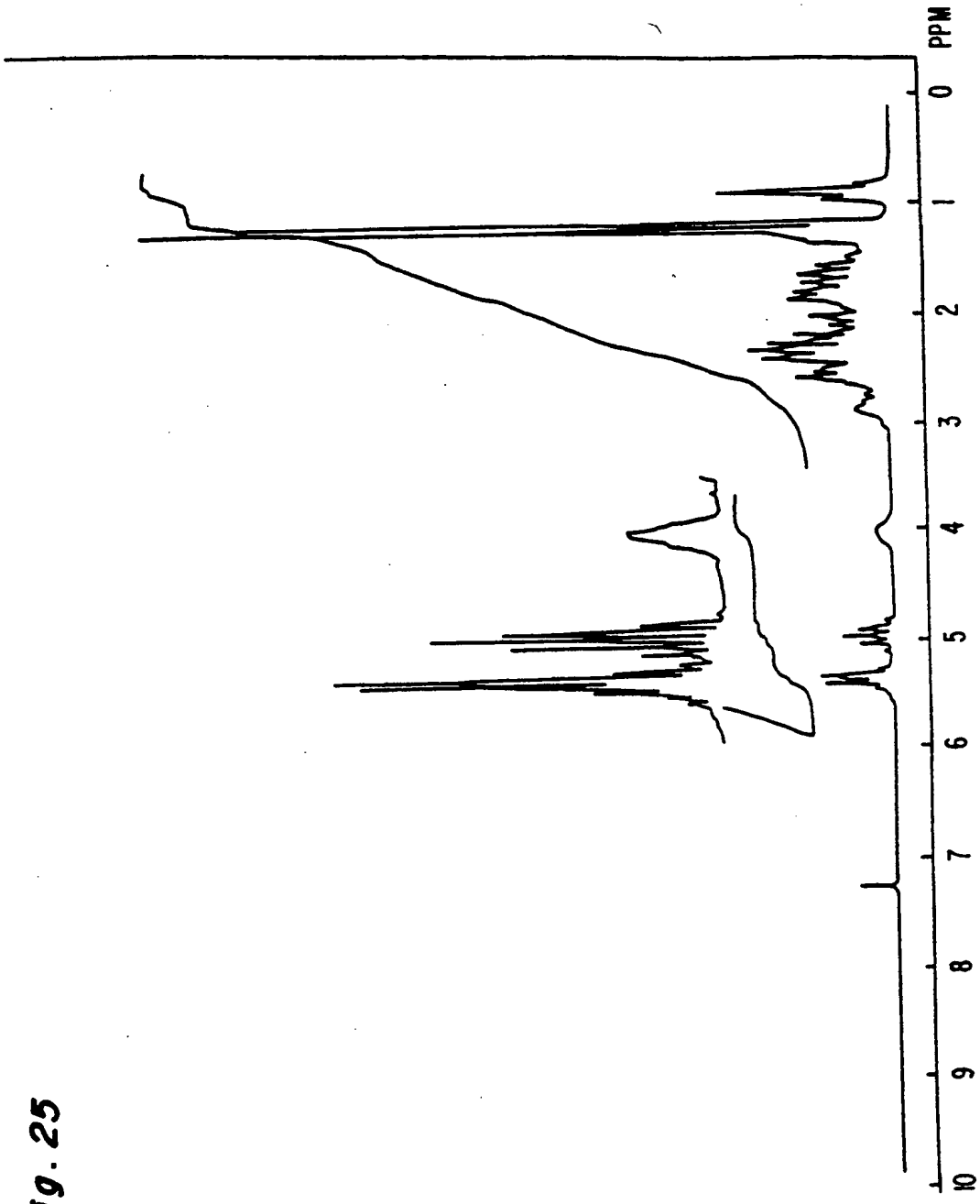


Fig. 25

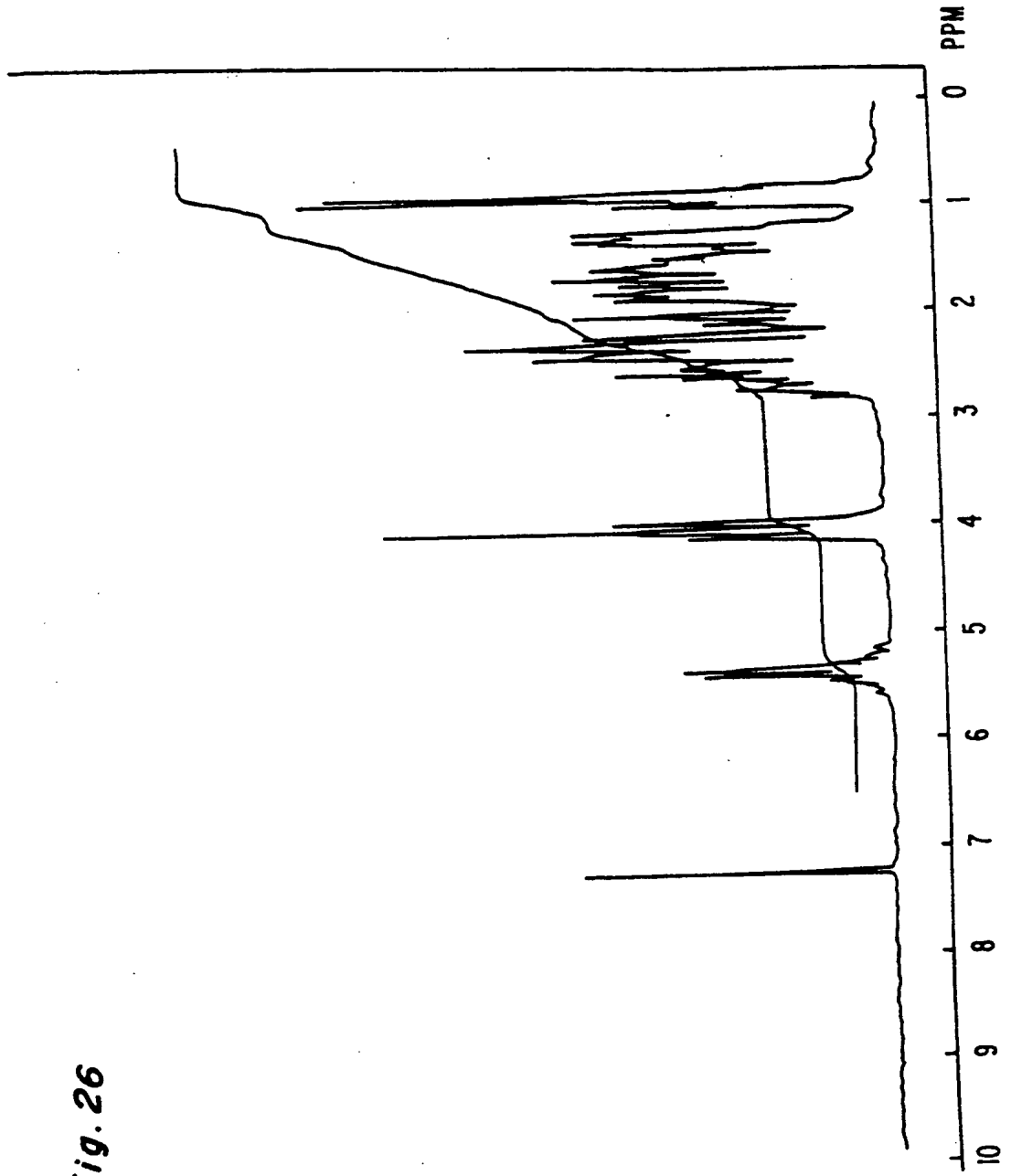


Fig. 26

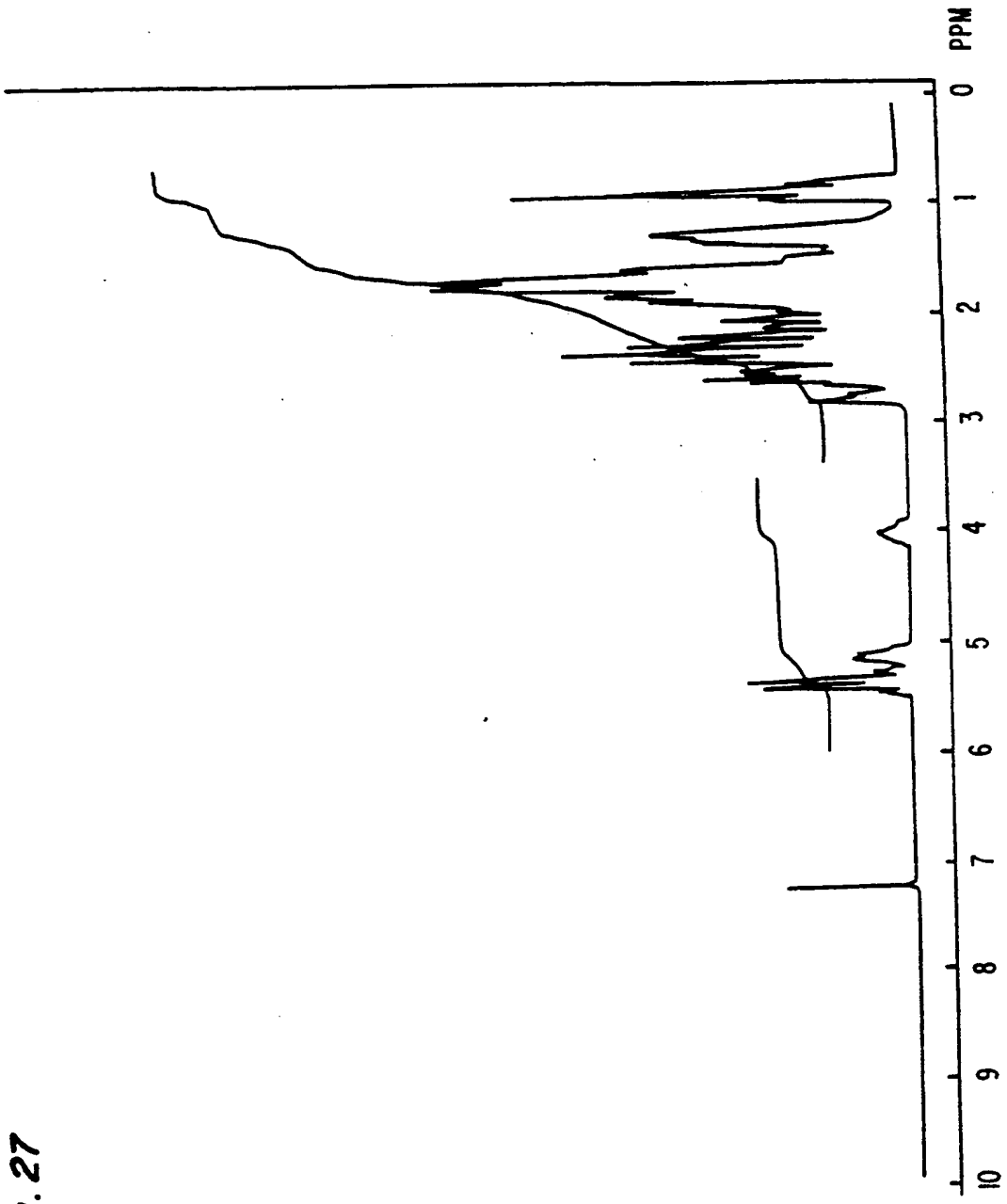


Fig. 27

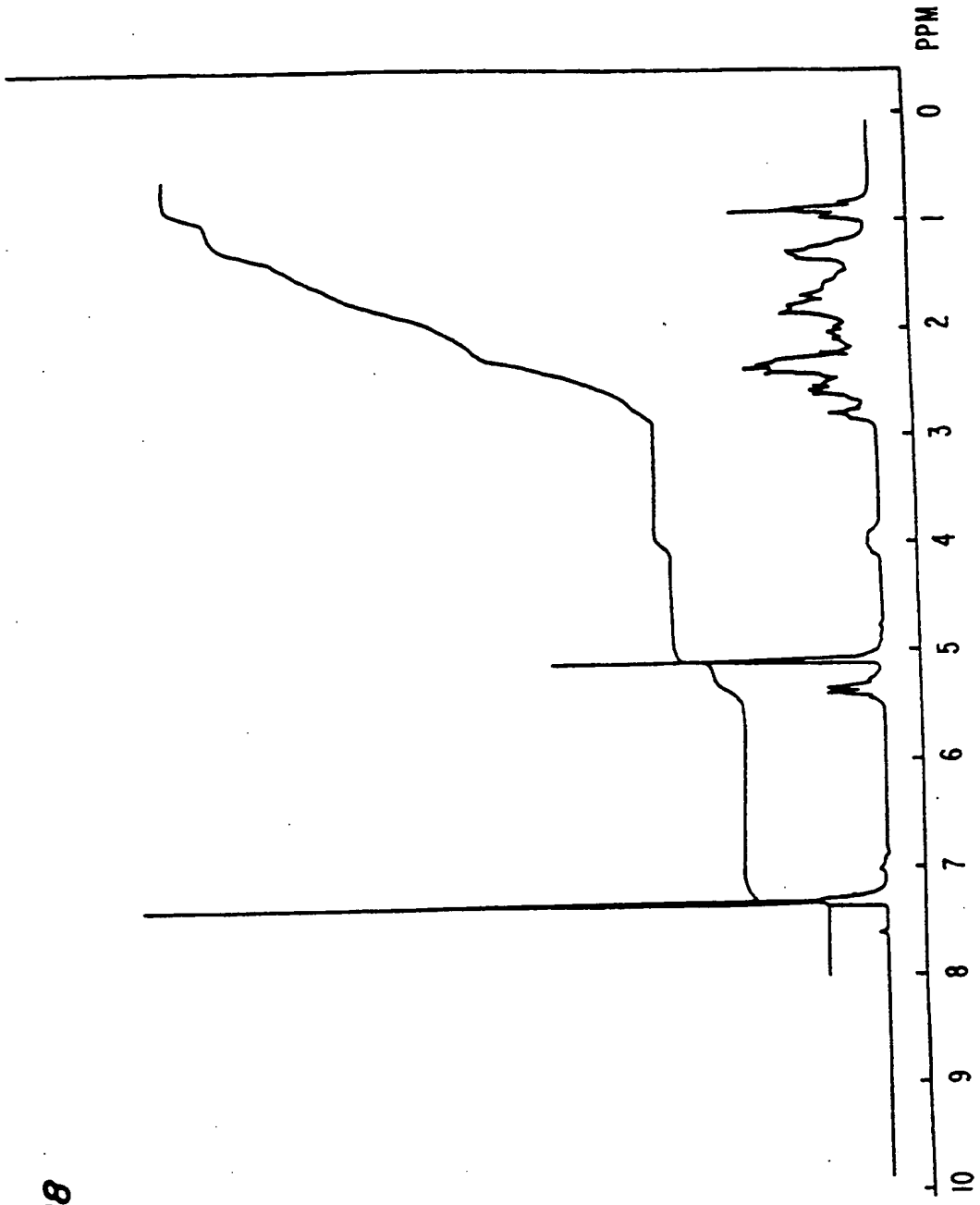


Fig. 28

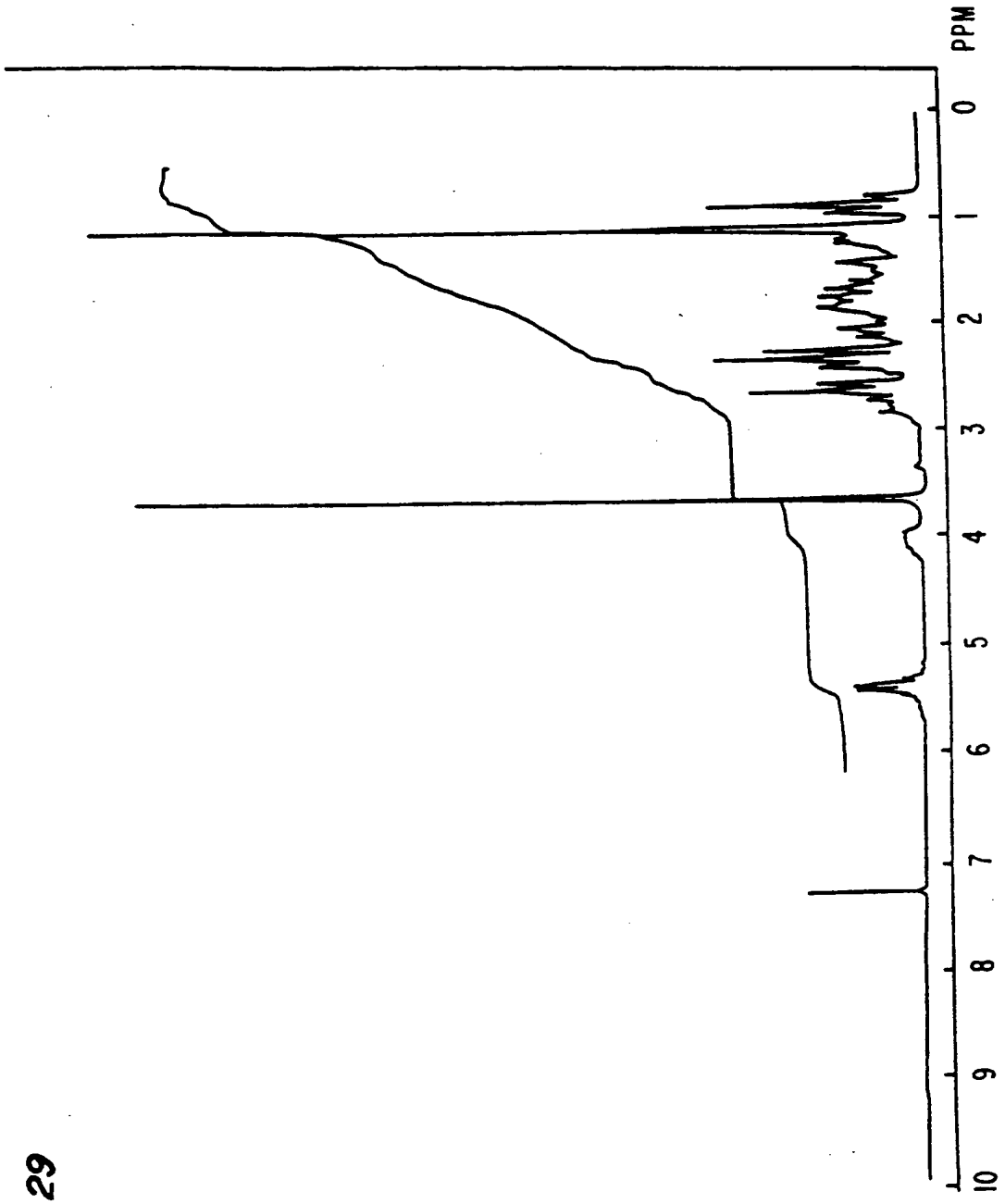


Fig. 29

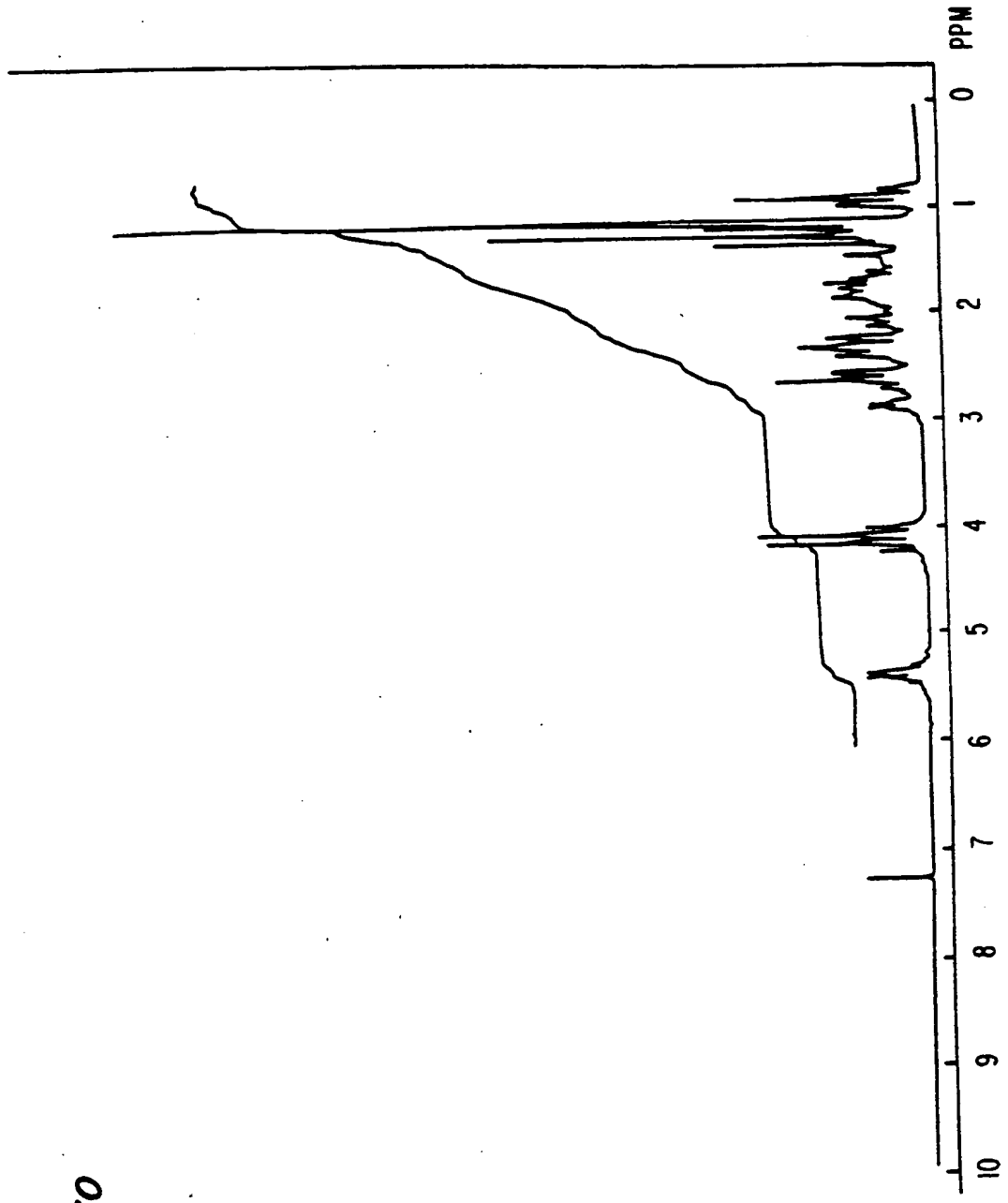
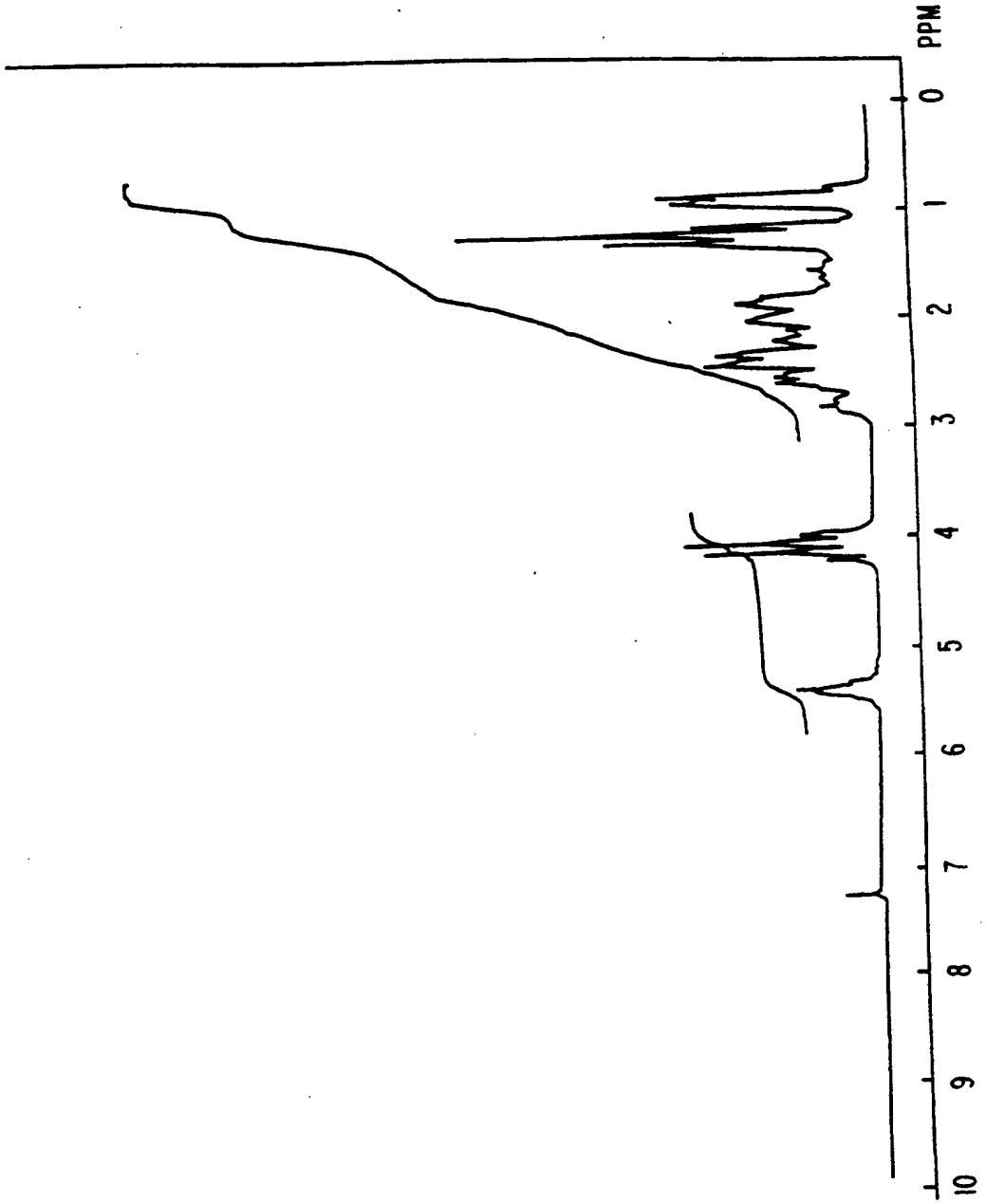


Fig. 30



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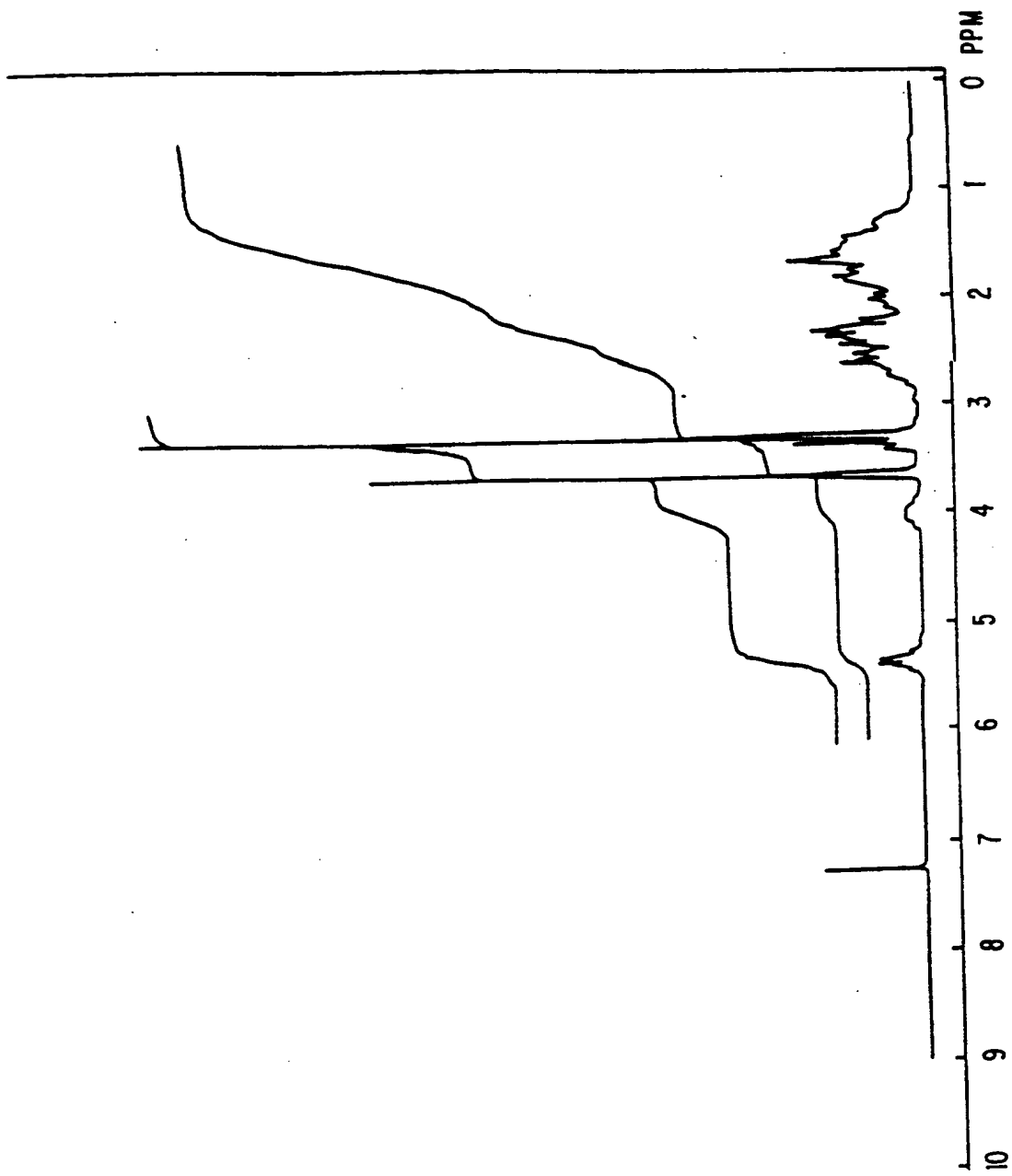


Fig. 32

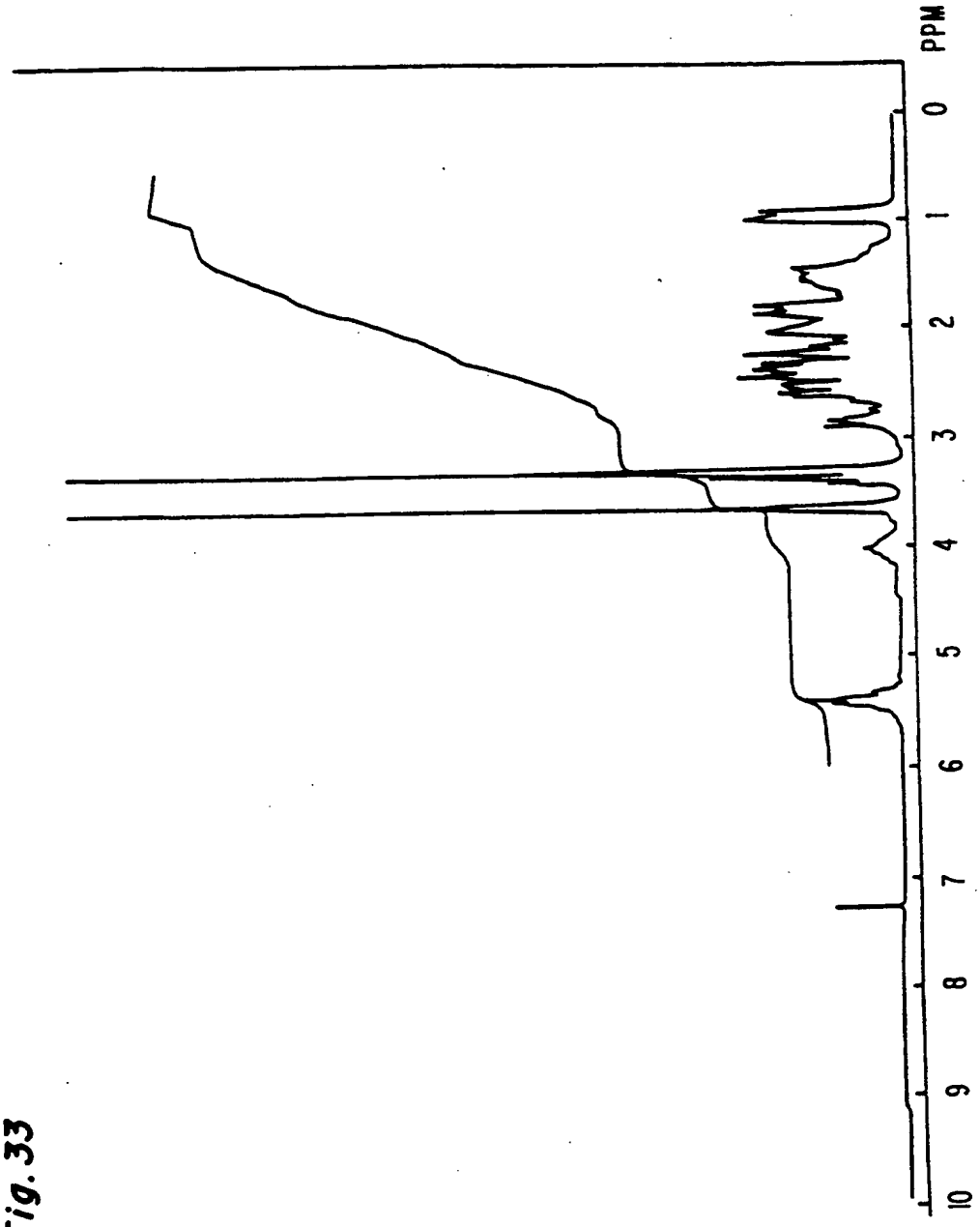


Fig. 33

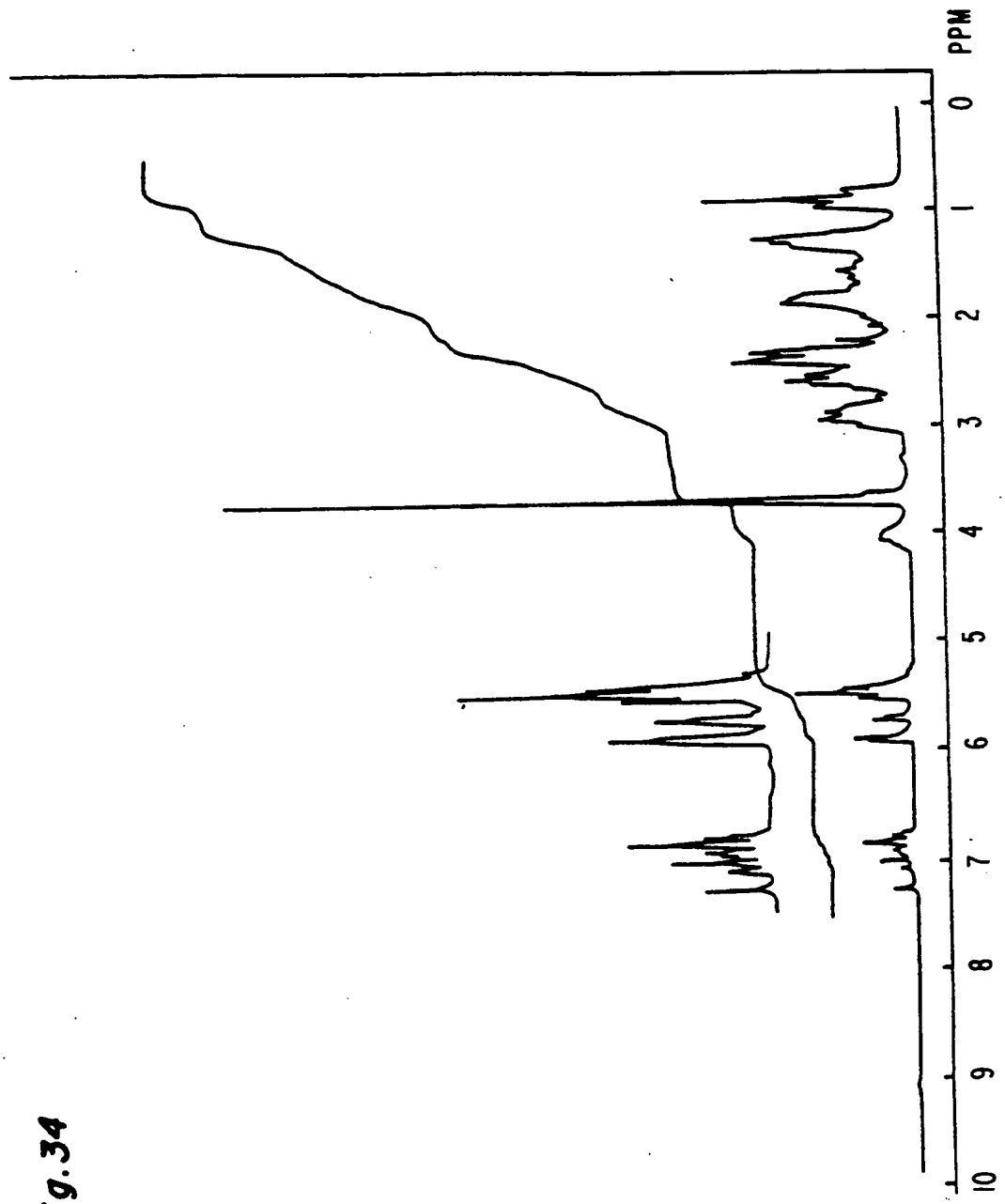


Fig.34

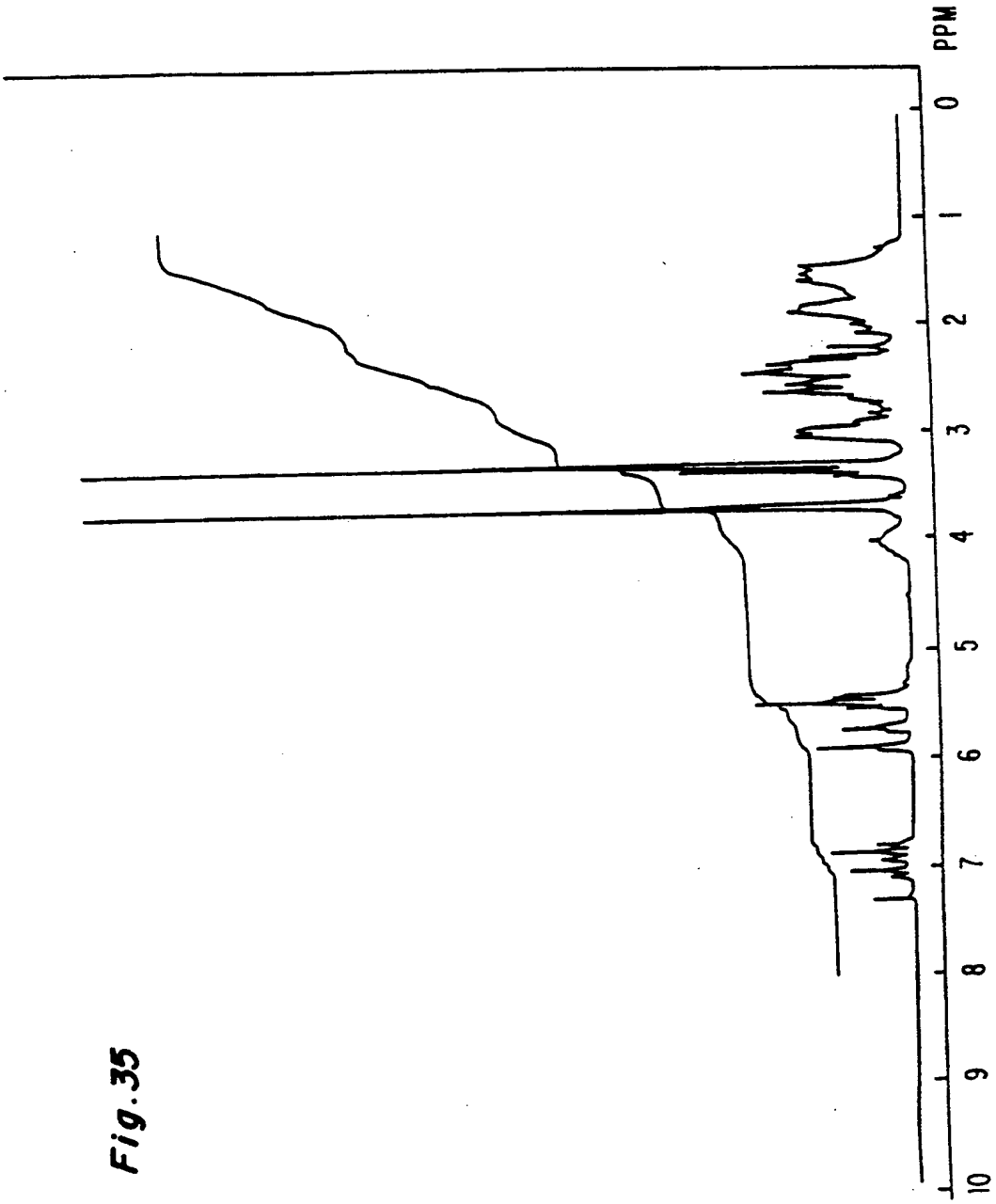


Fig. 35

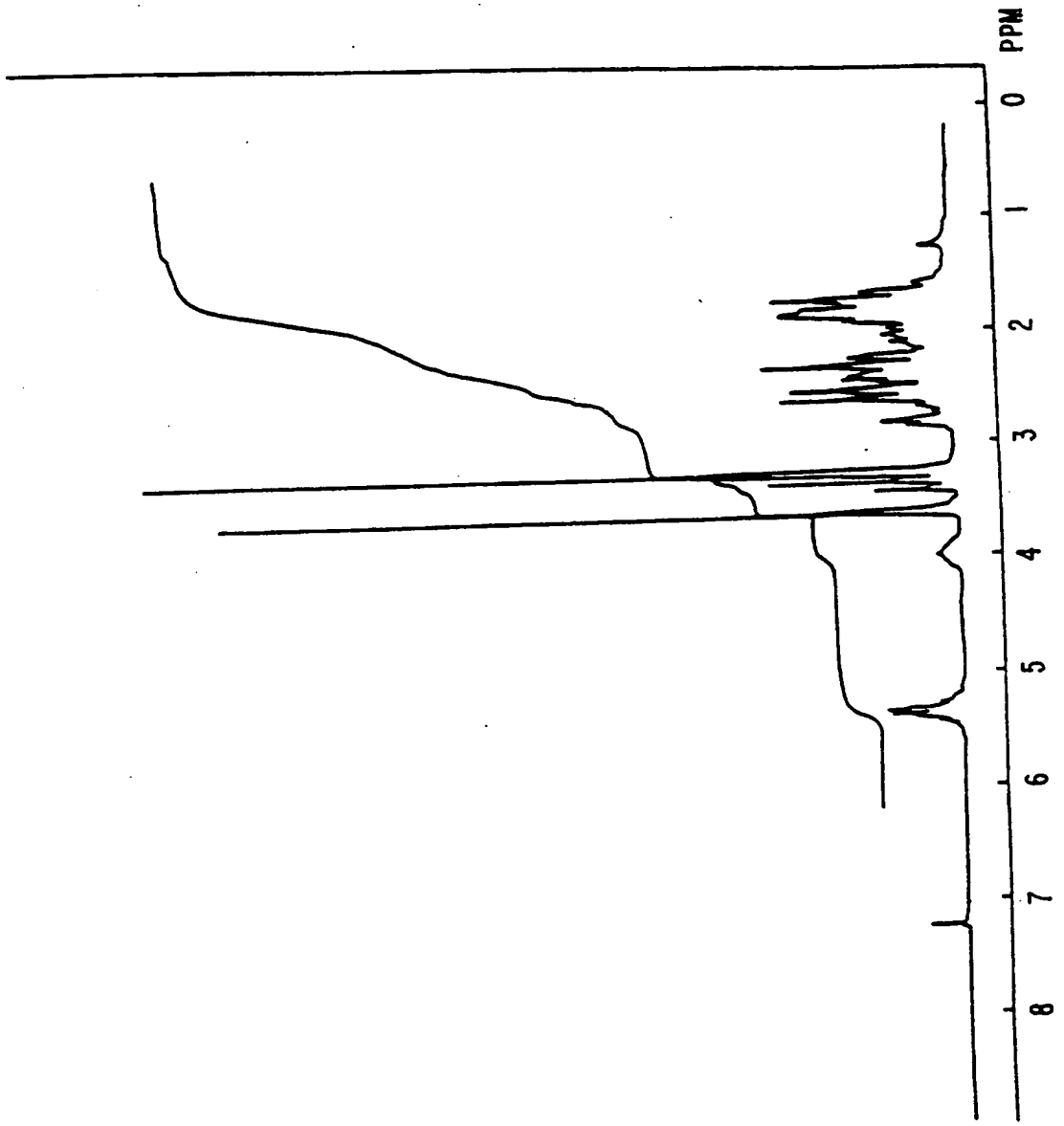


Fig. 36

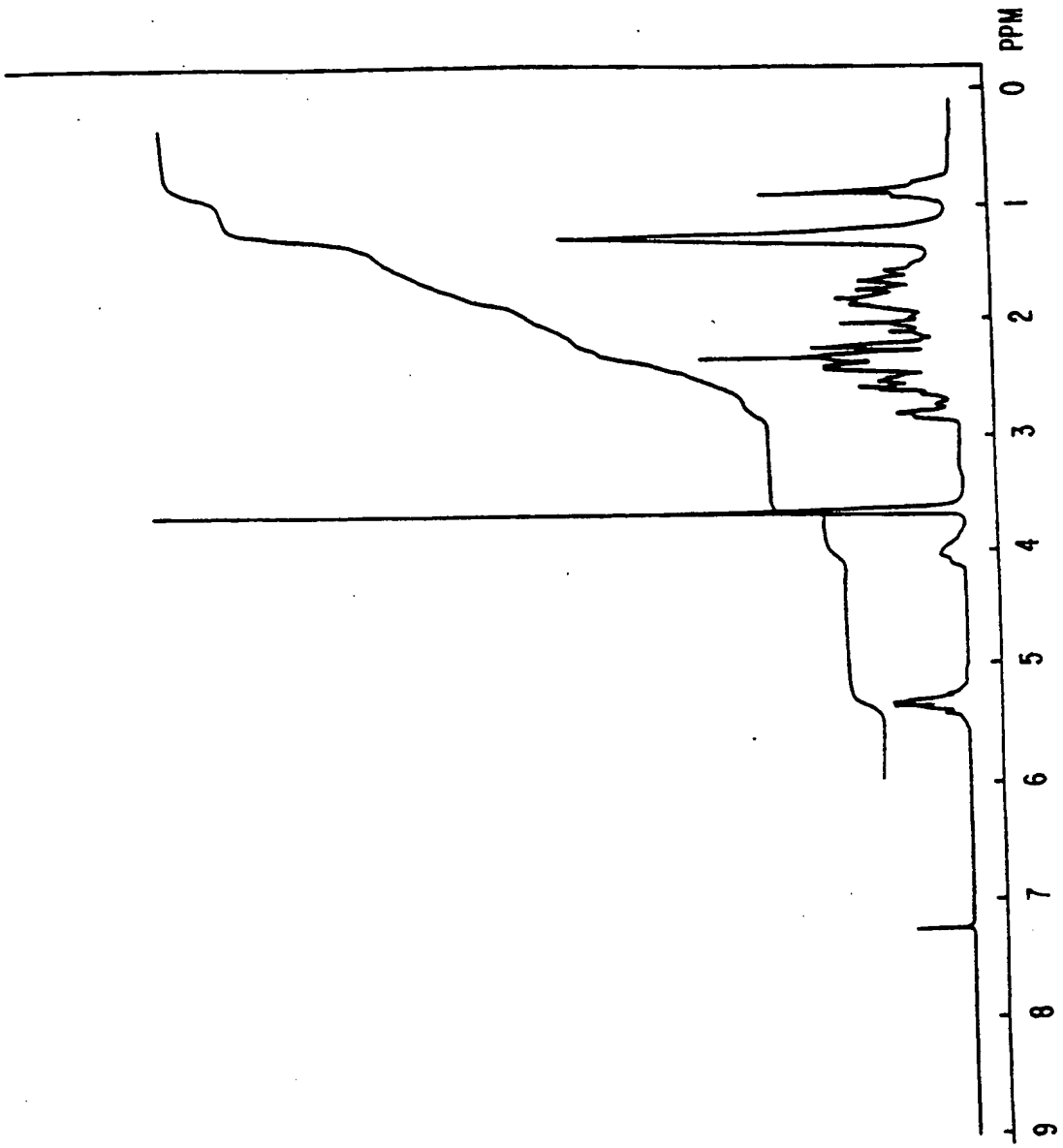


Fig.37

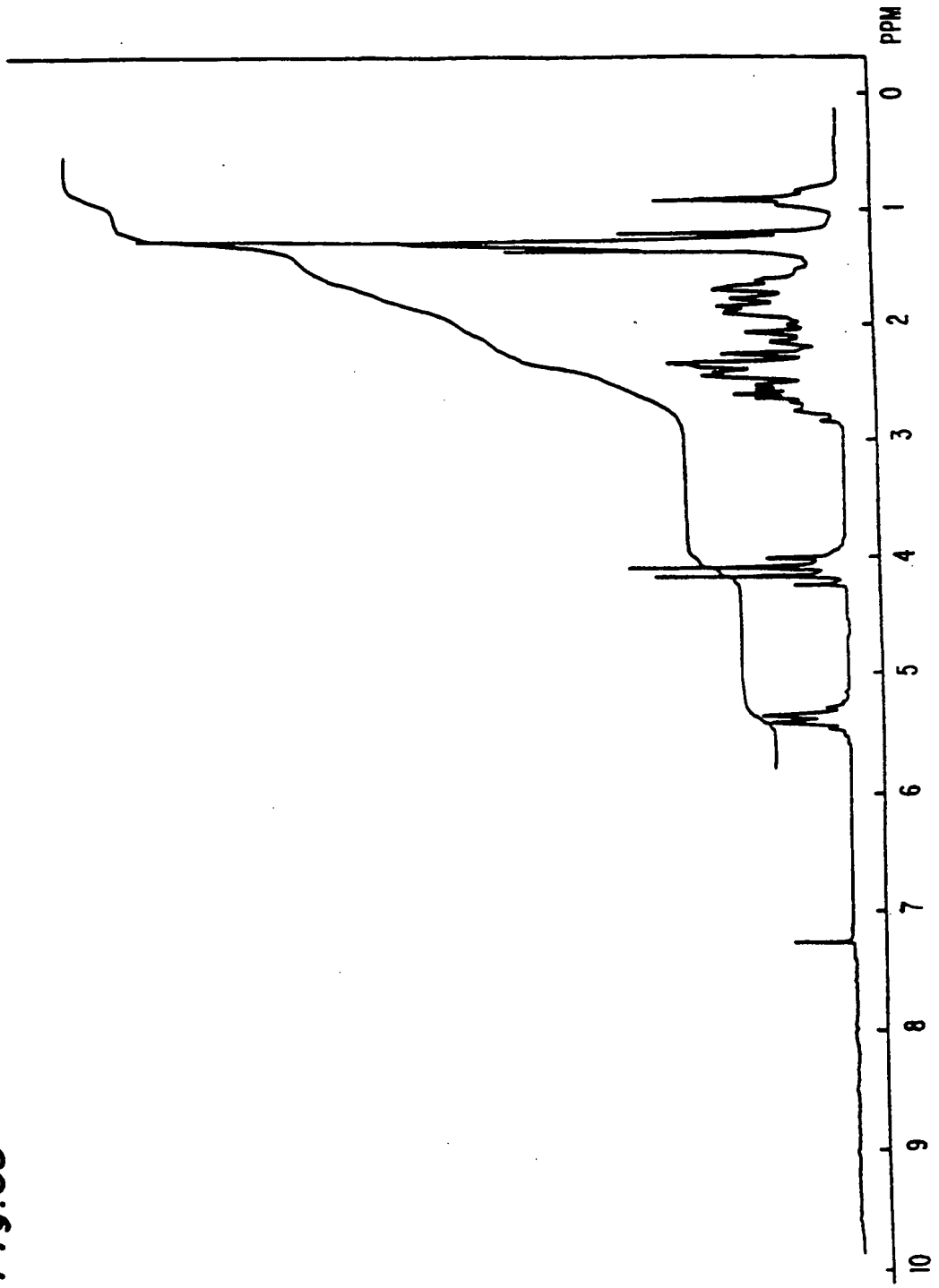


Fig. 38

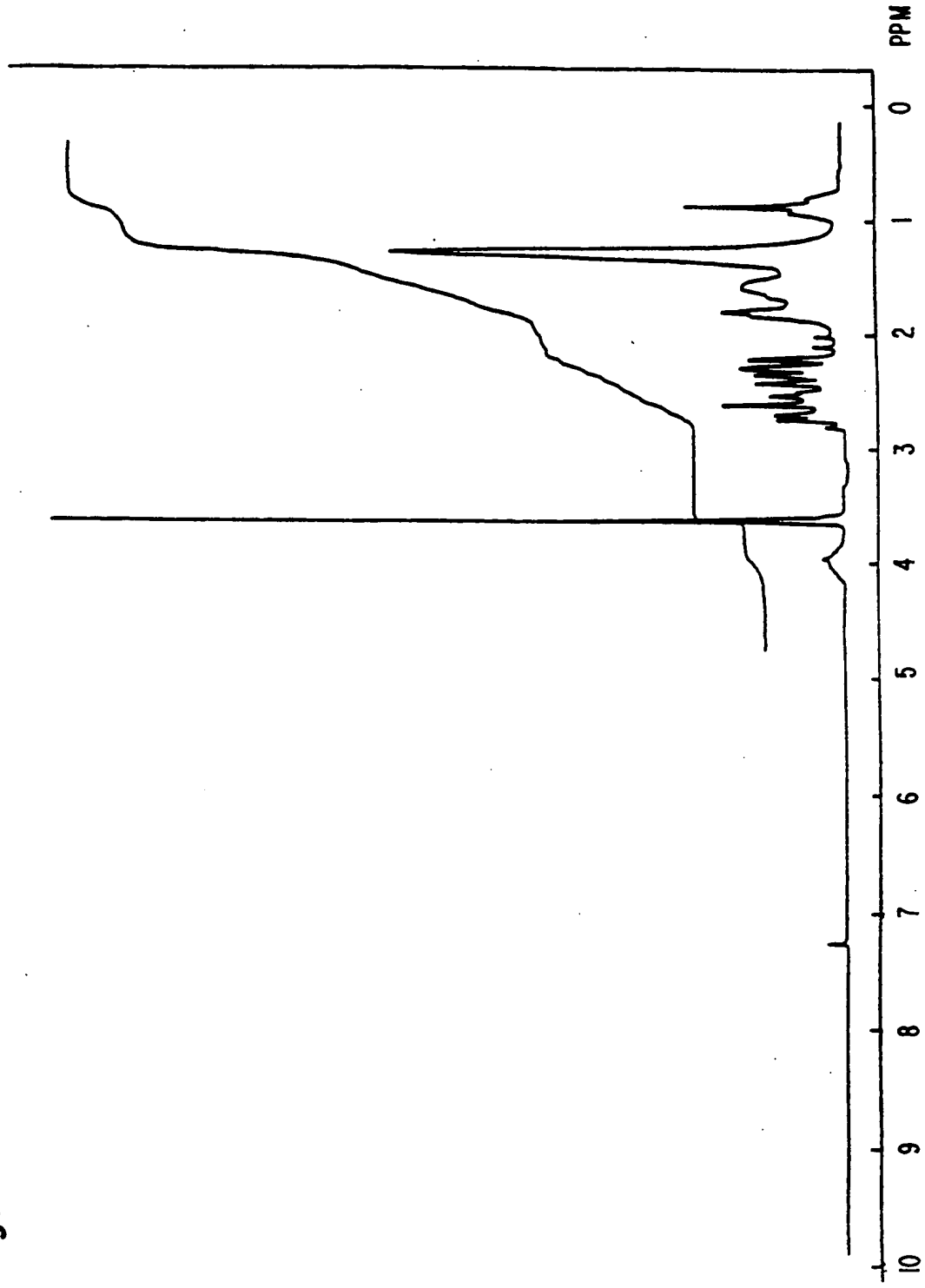


Fig.39

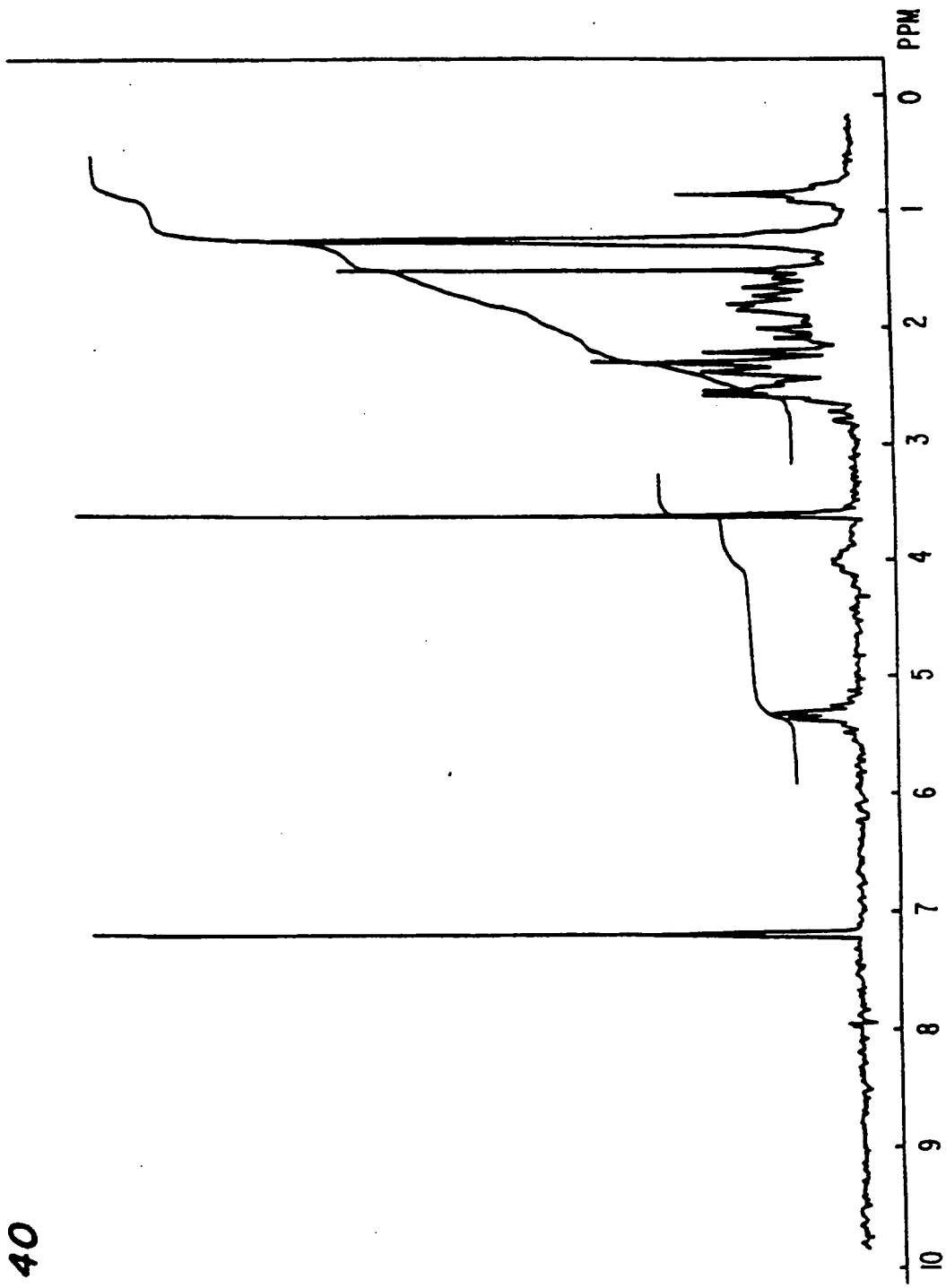


Fig. 40

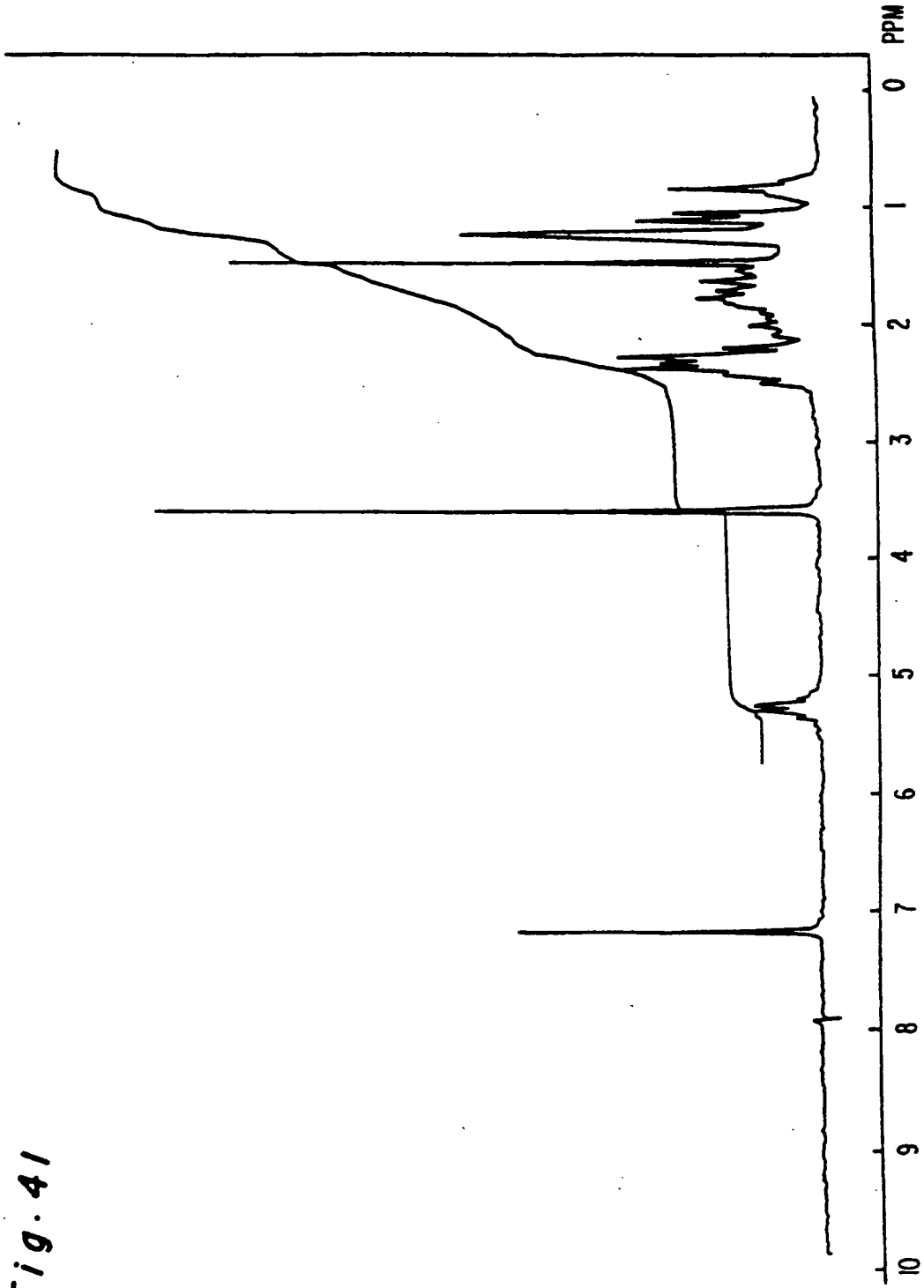


Fig. 41

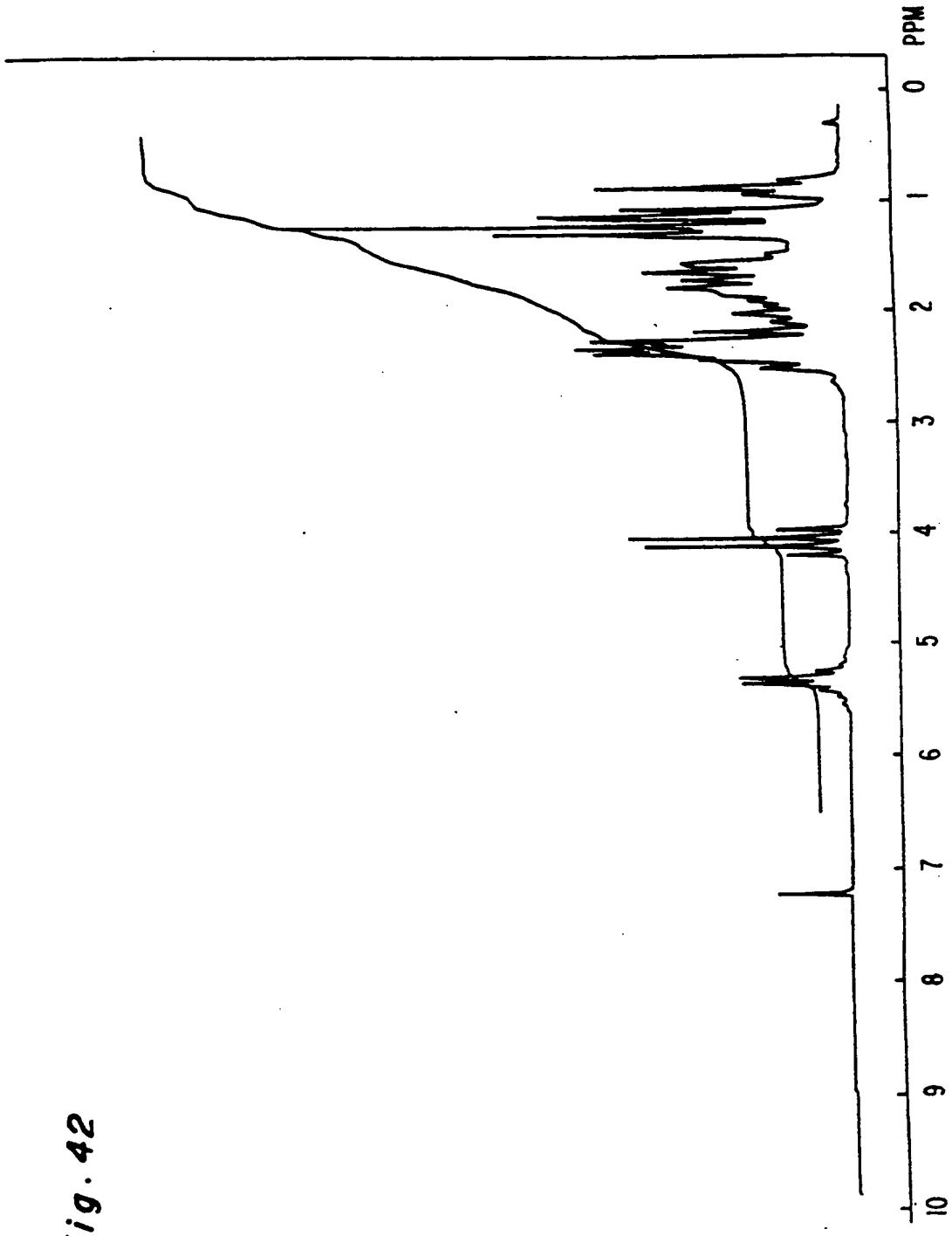


Fig. 42

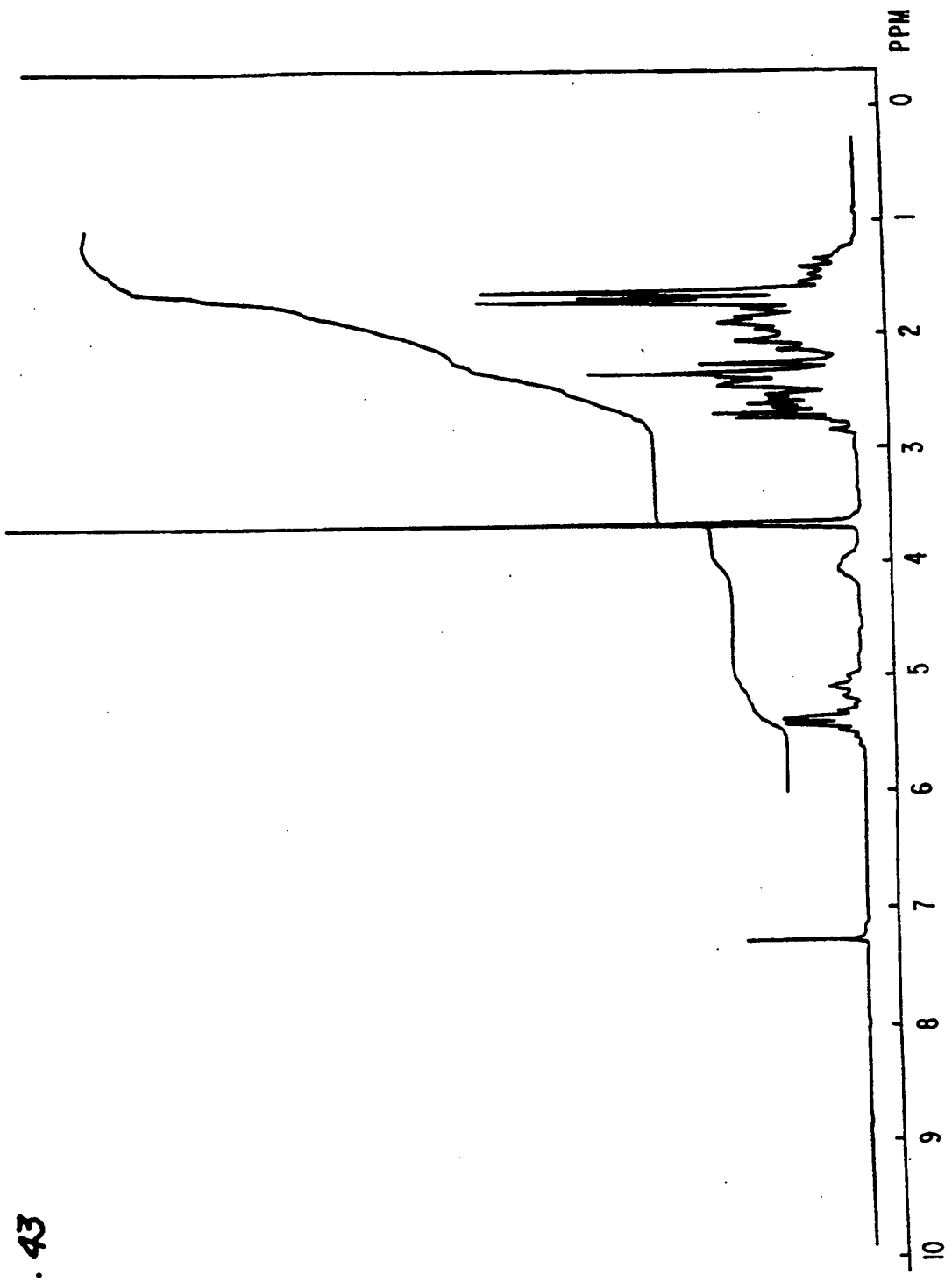


Fig. 43

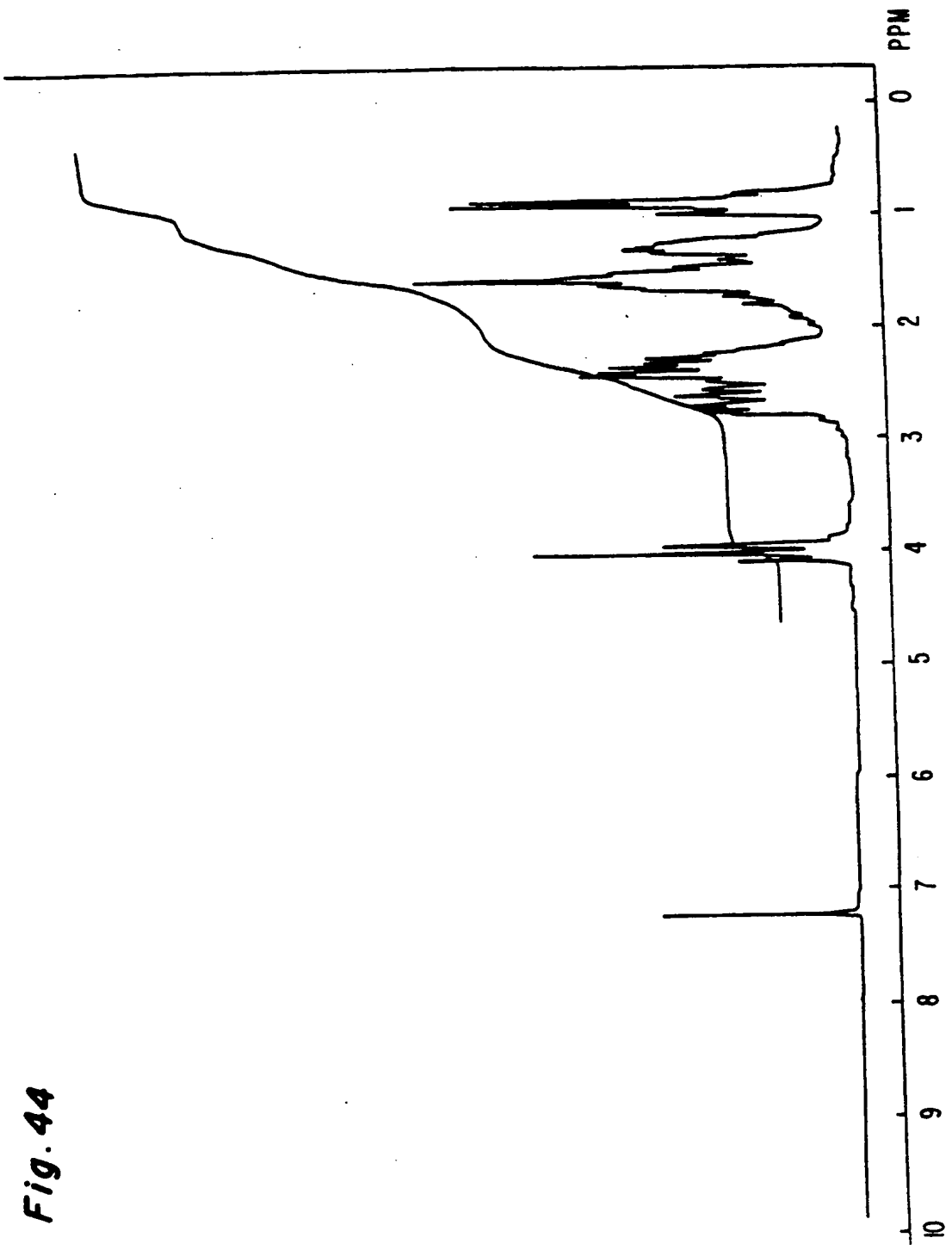


Fig. 44

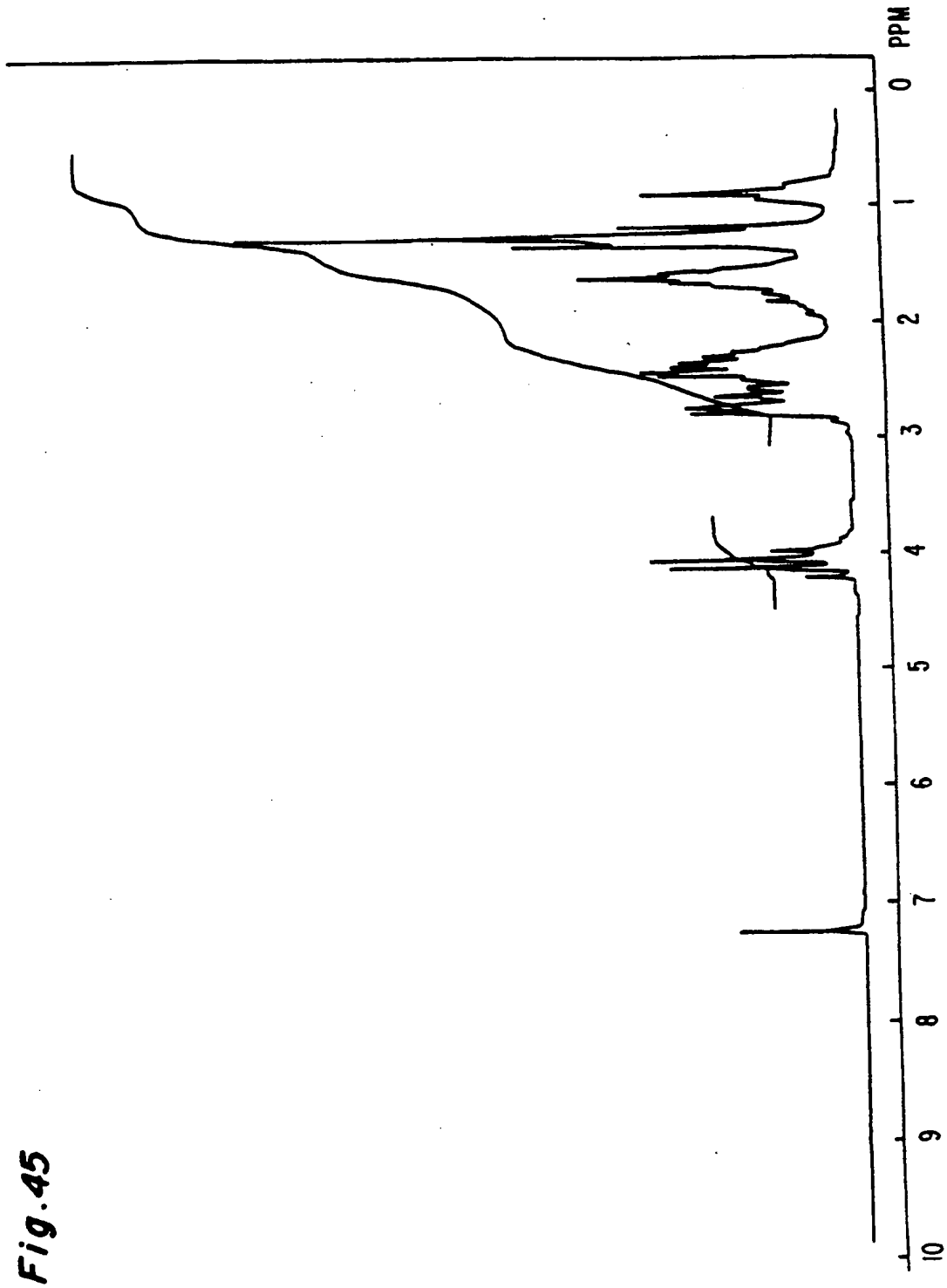


Fig.45

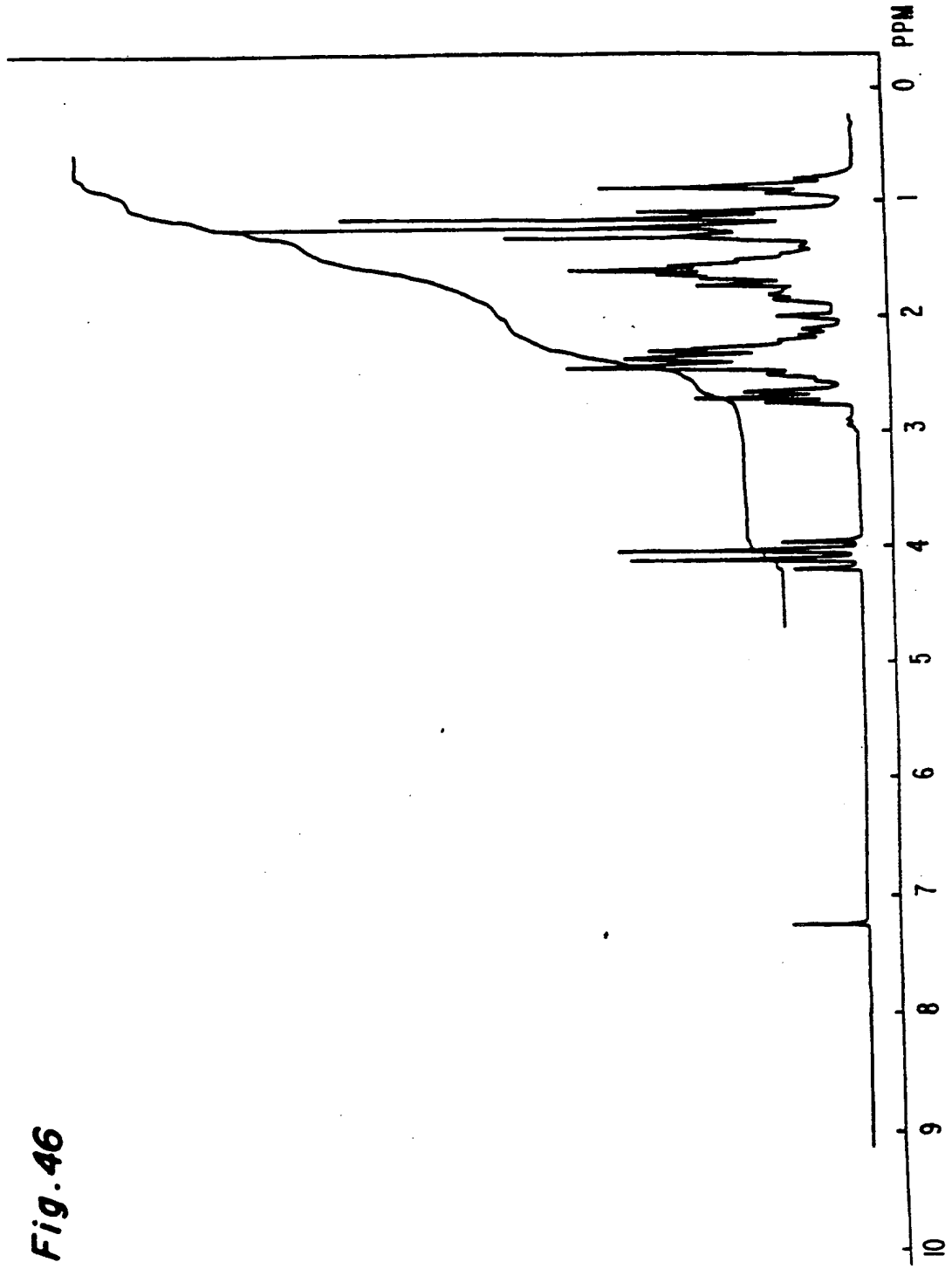


Fig. 46

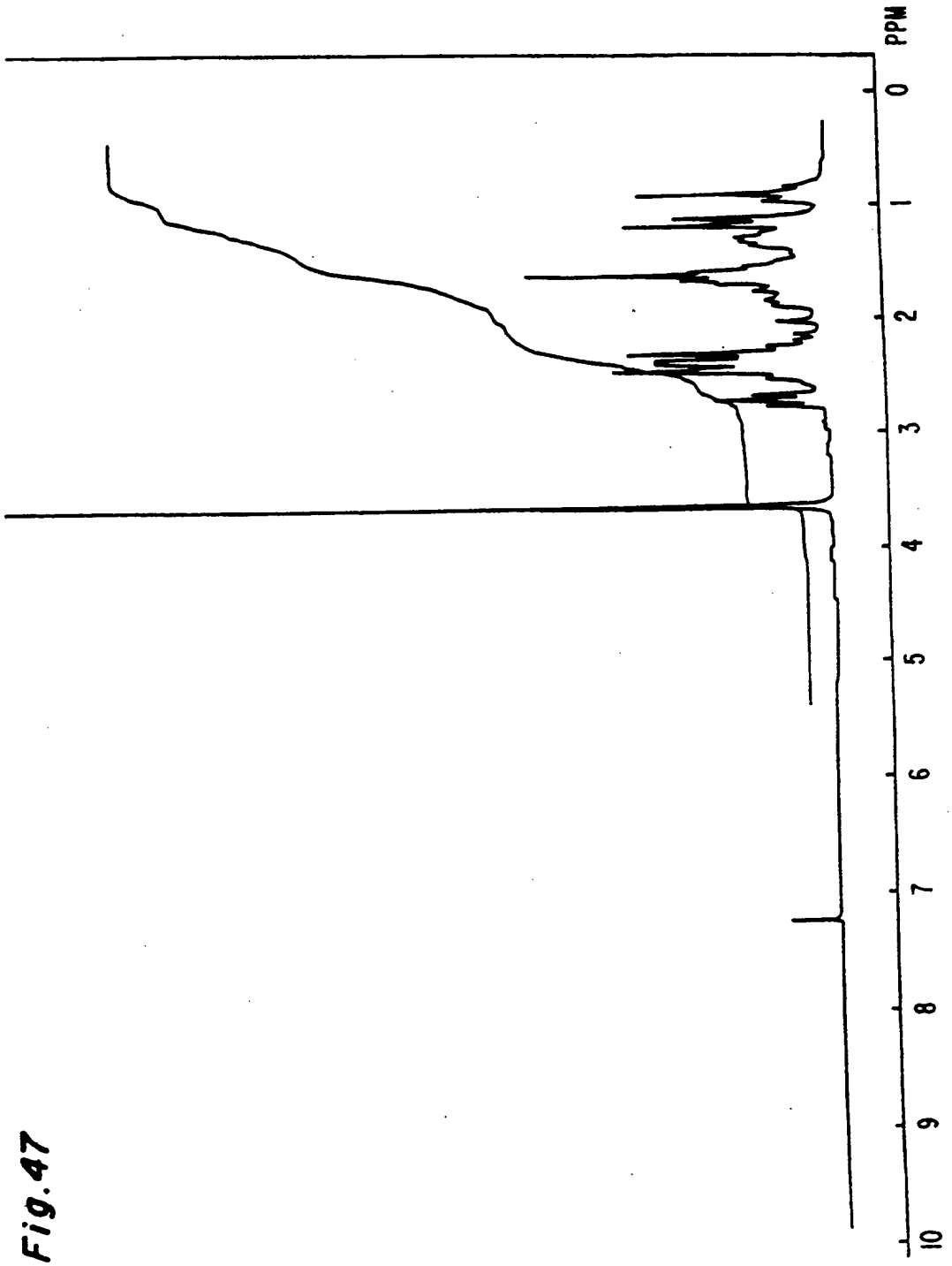


Fig.47

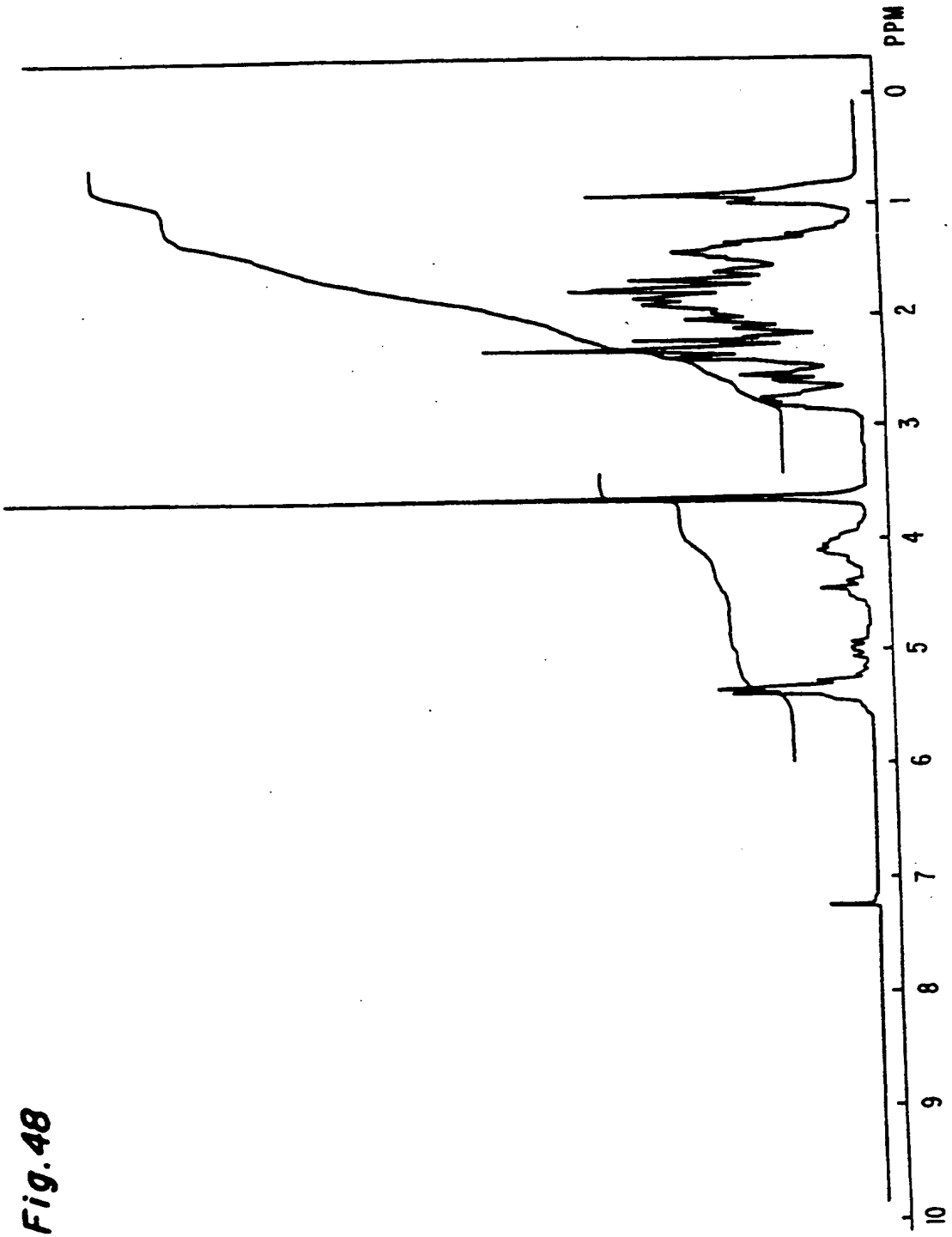


Fig. 48

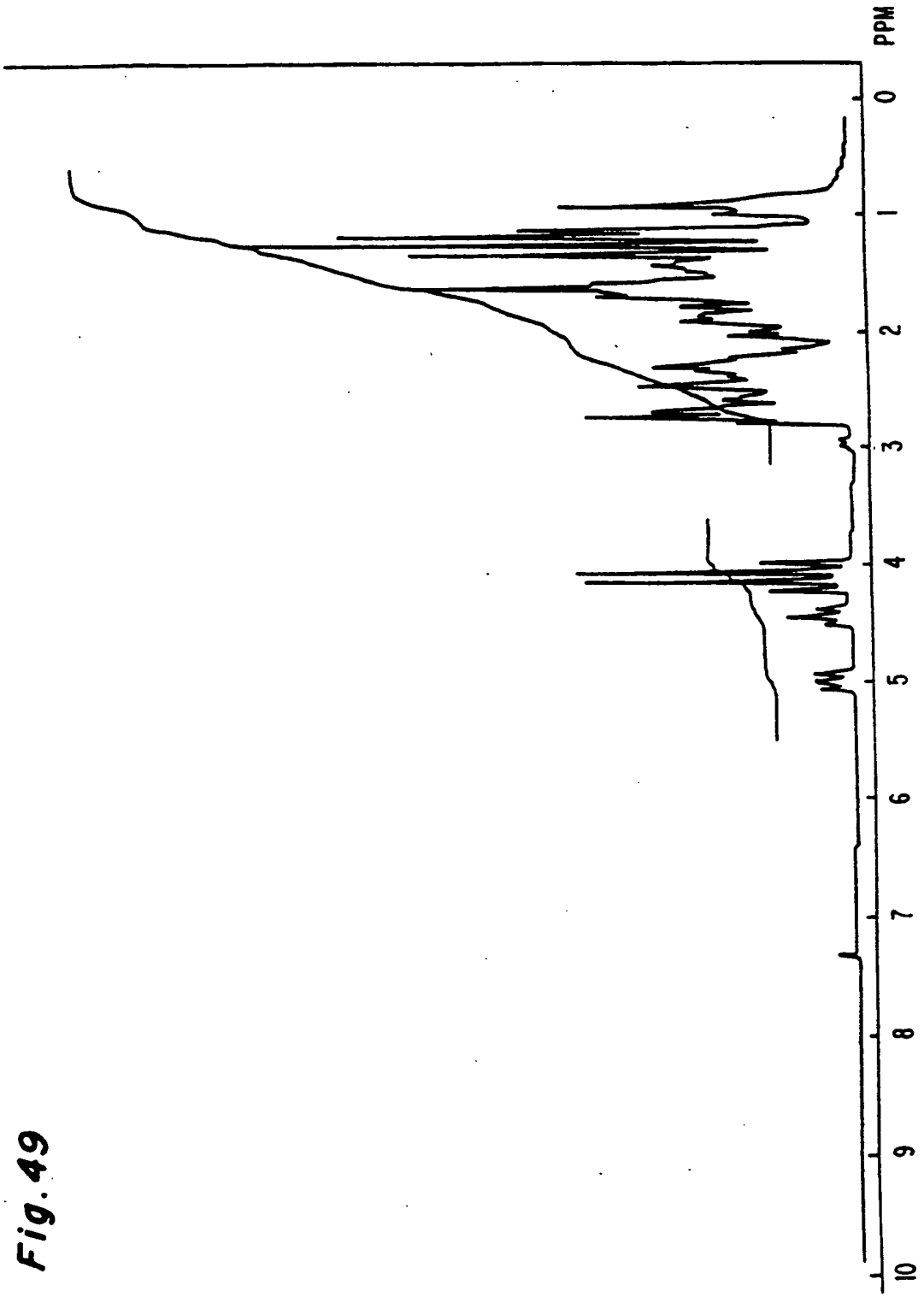


Fig. 49

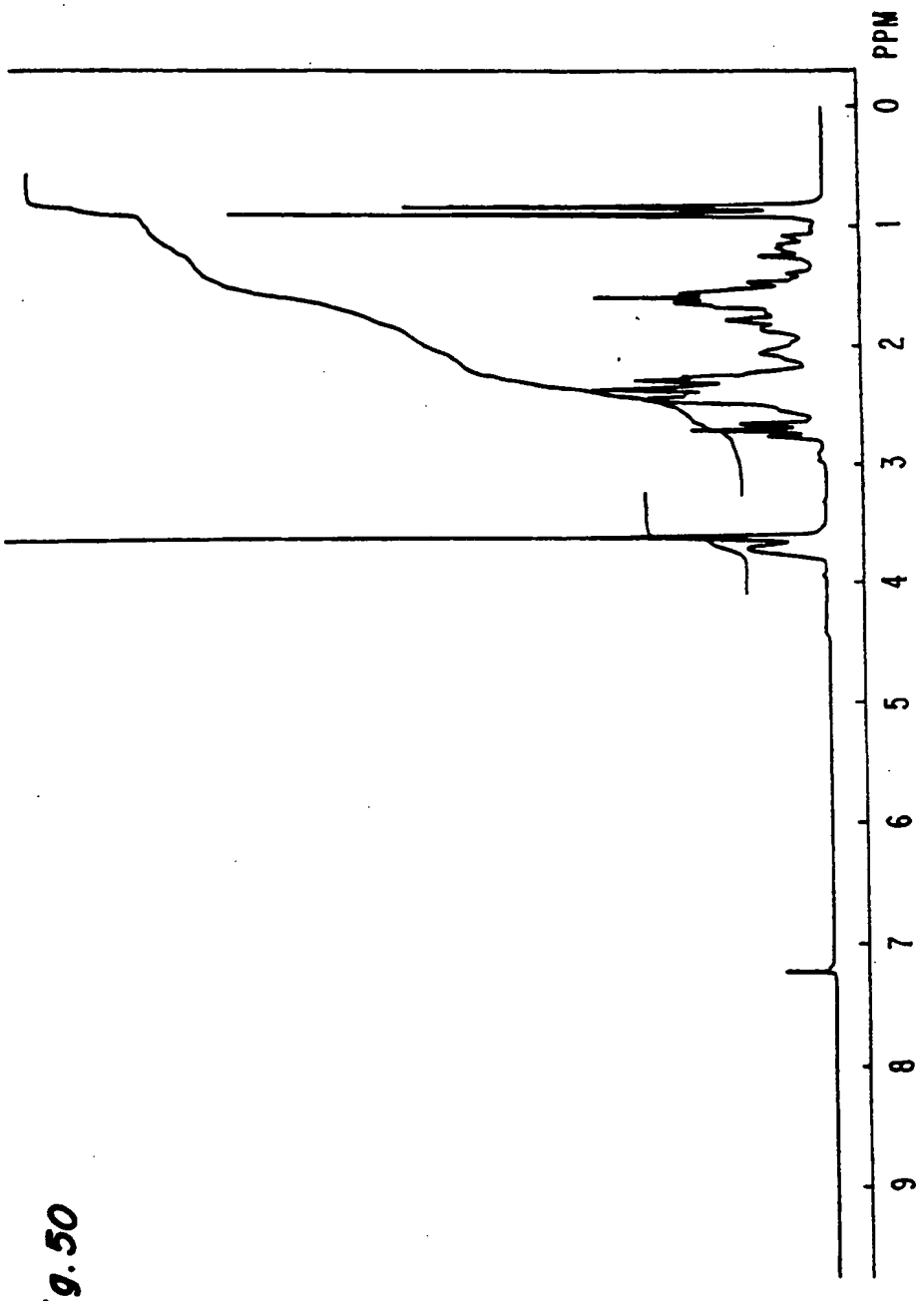


Fig. 50

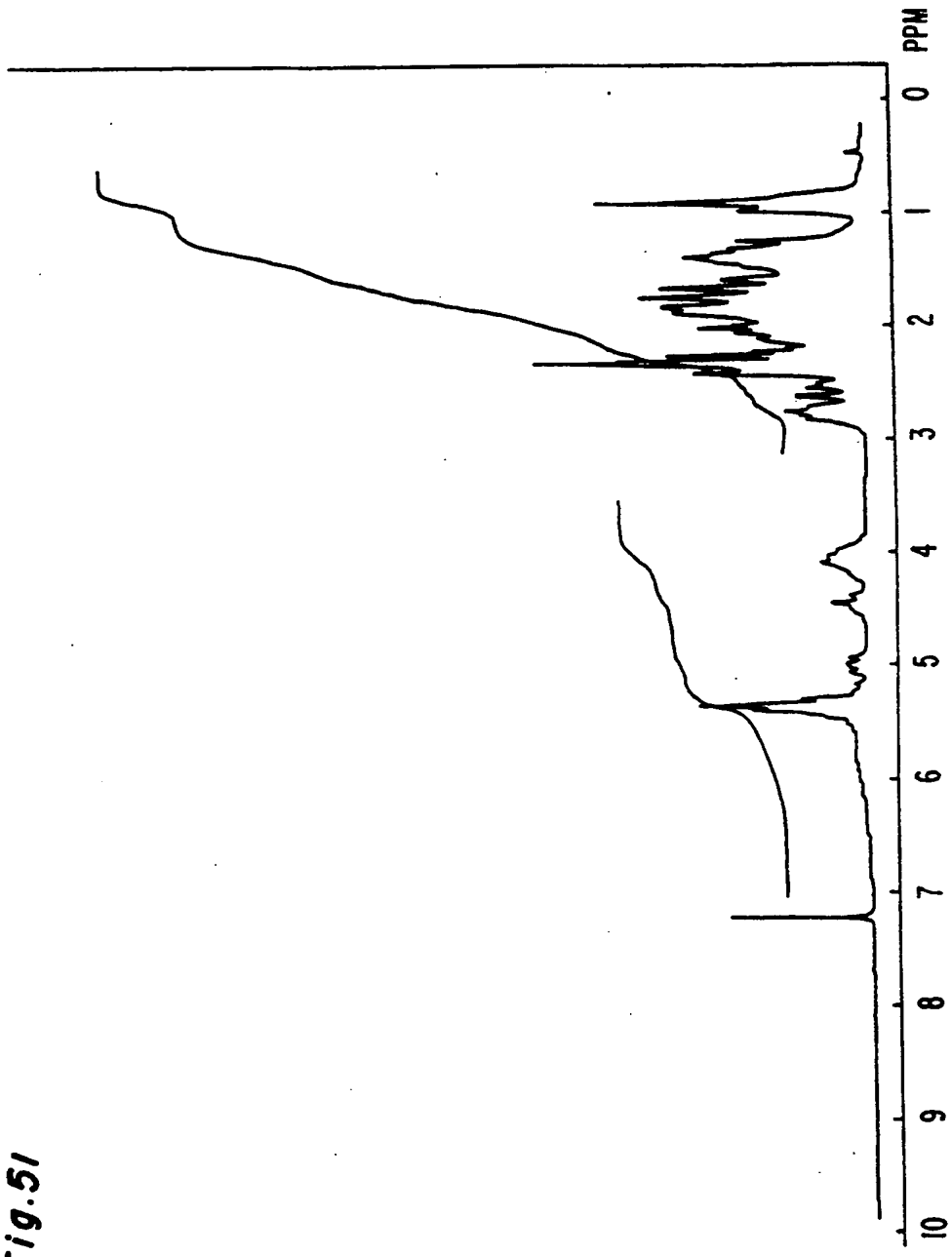


Fig.51

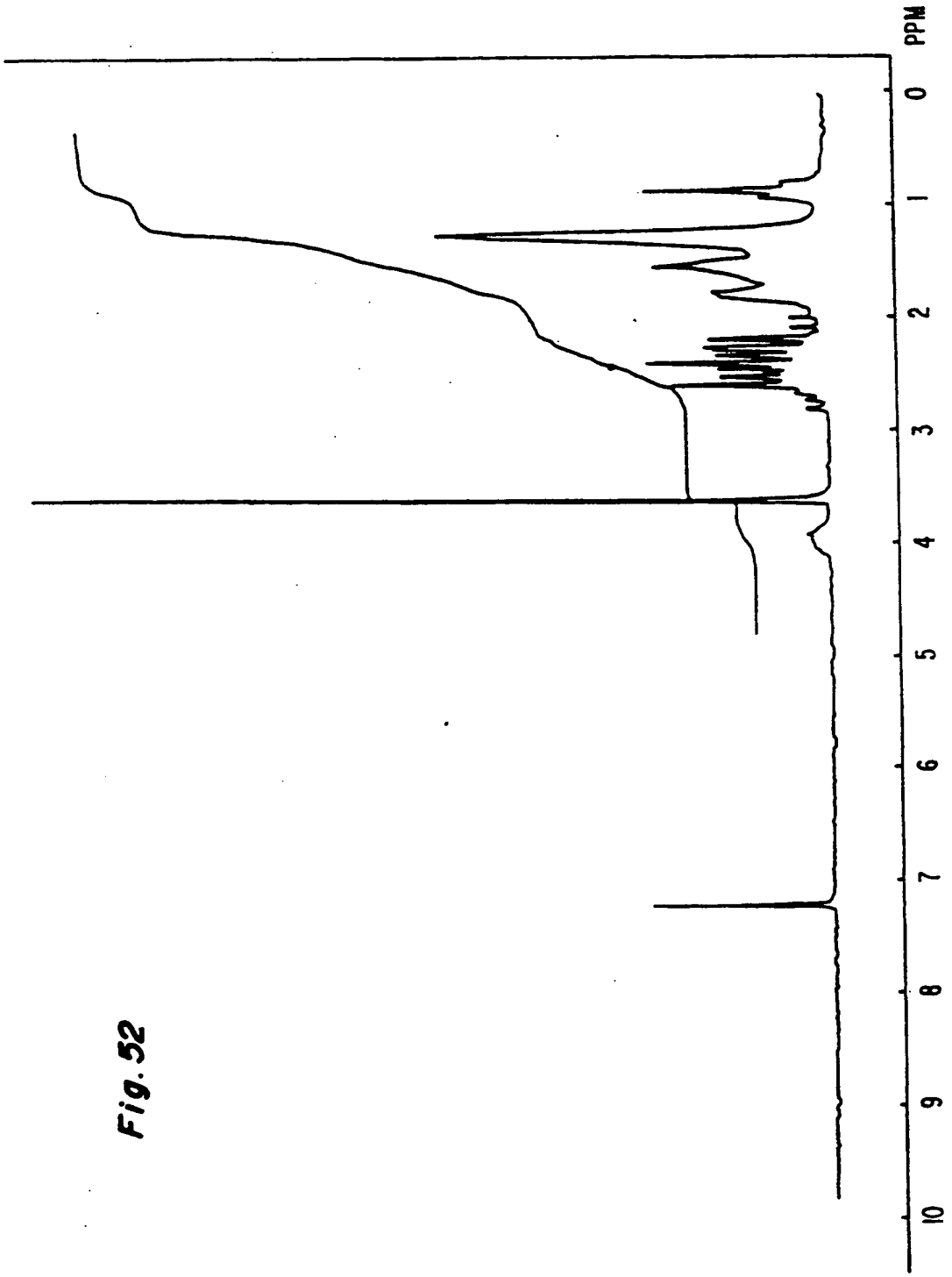


Fig. 52

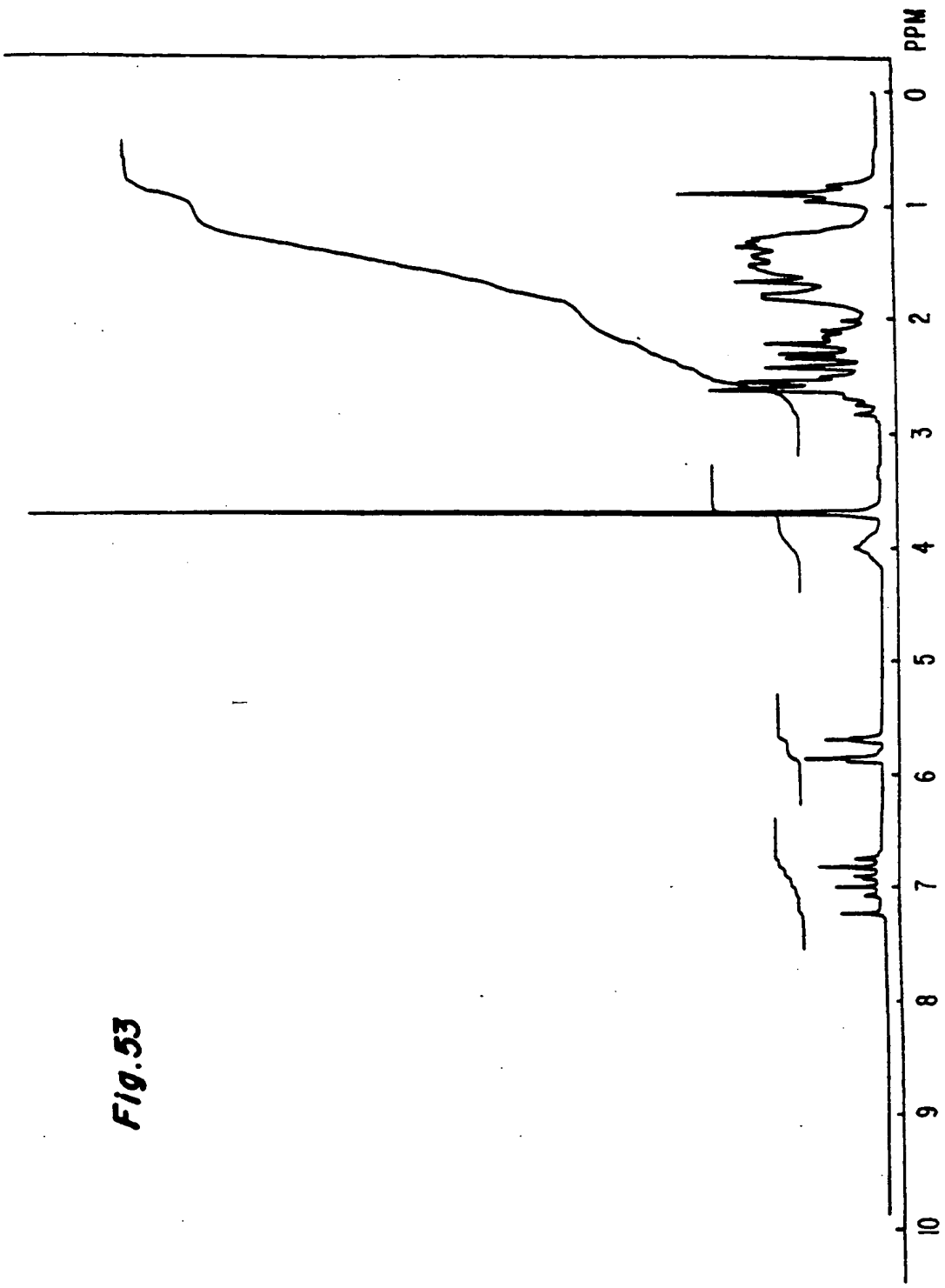


Fig. 53

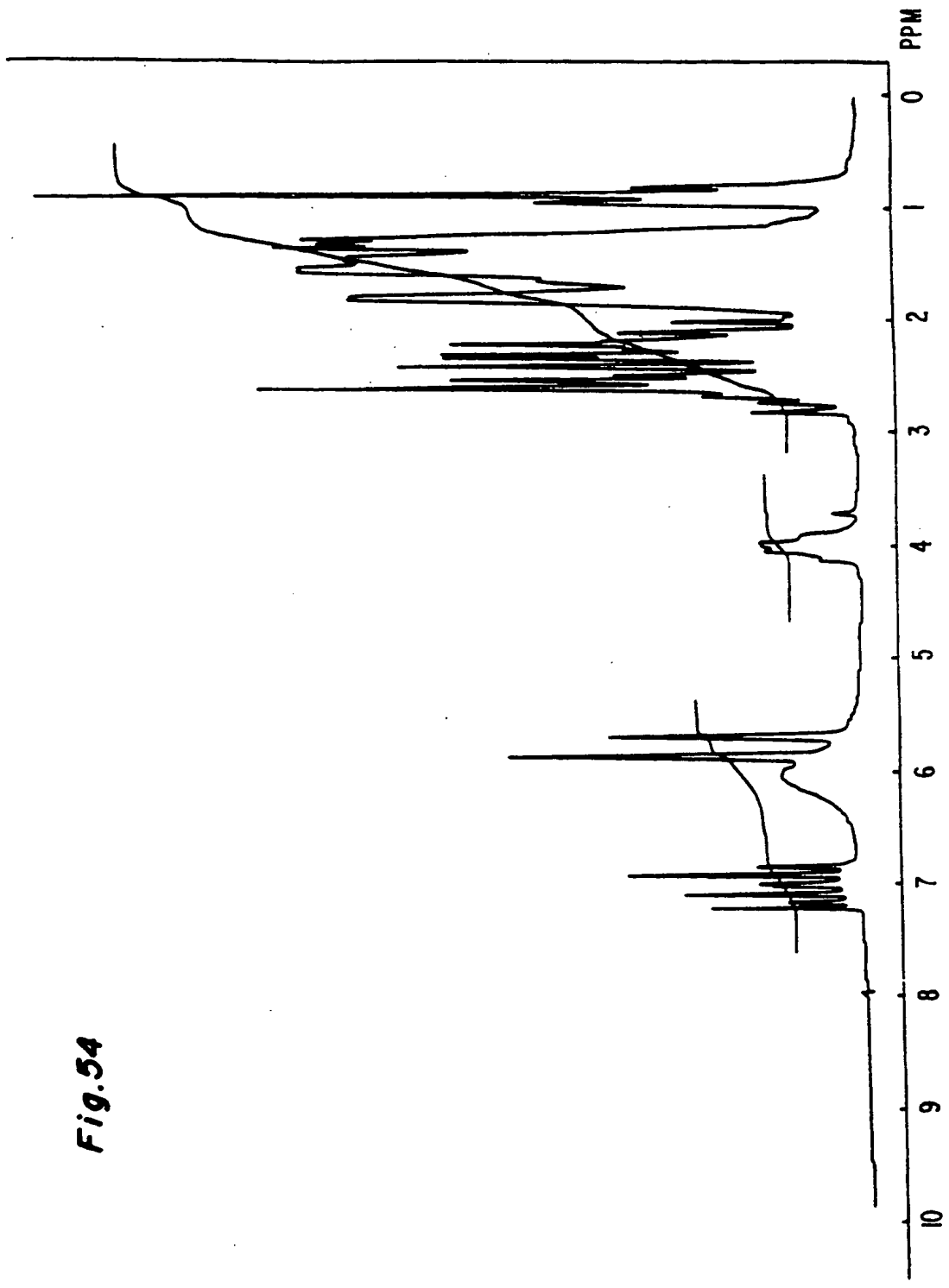


Fig.54

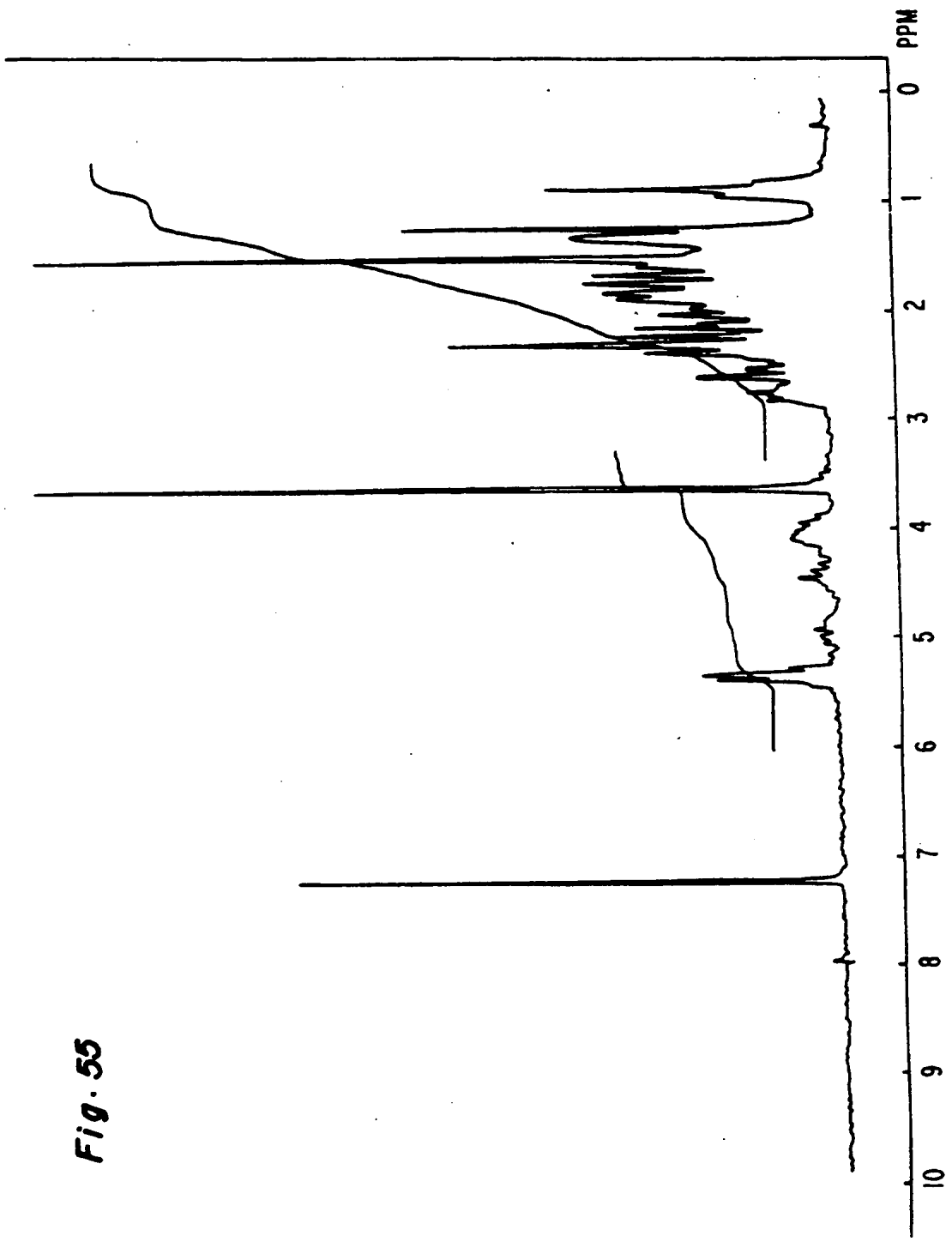


Fig. 55

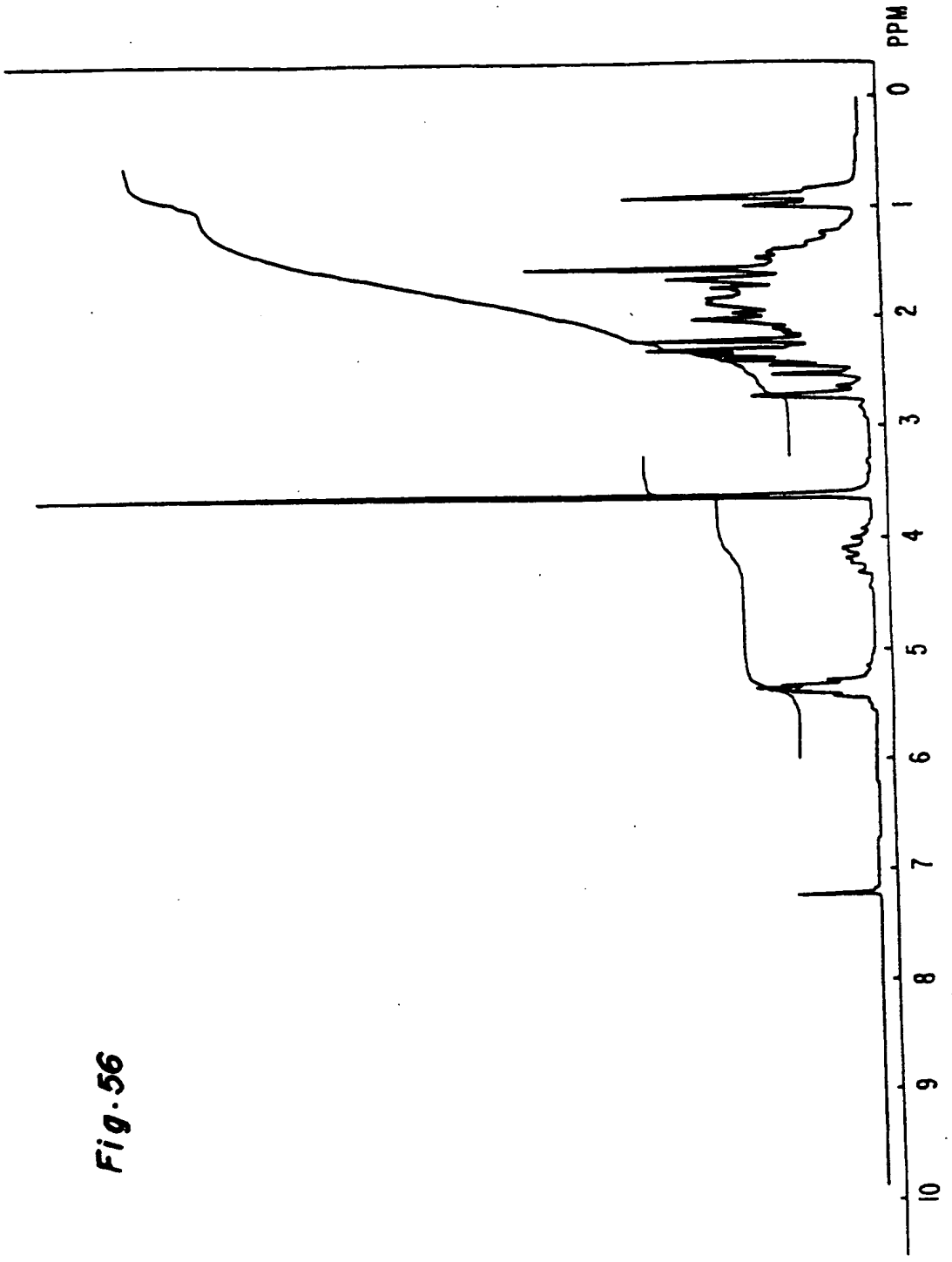


Fig. 56

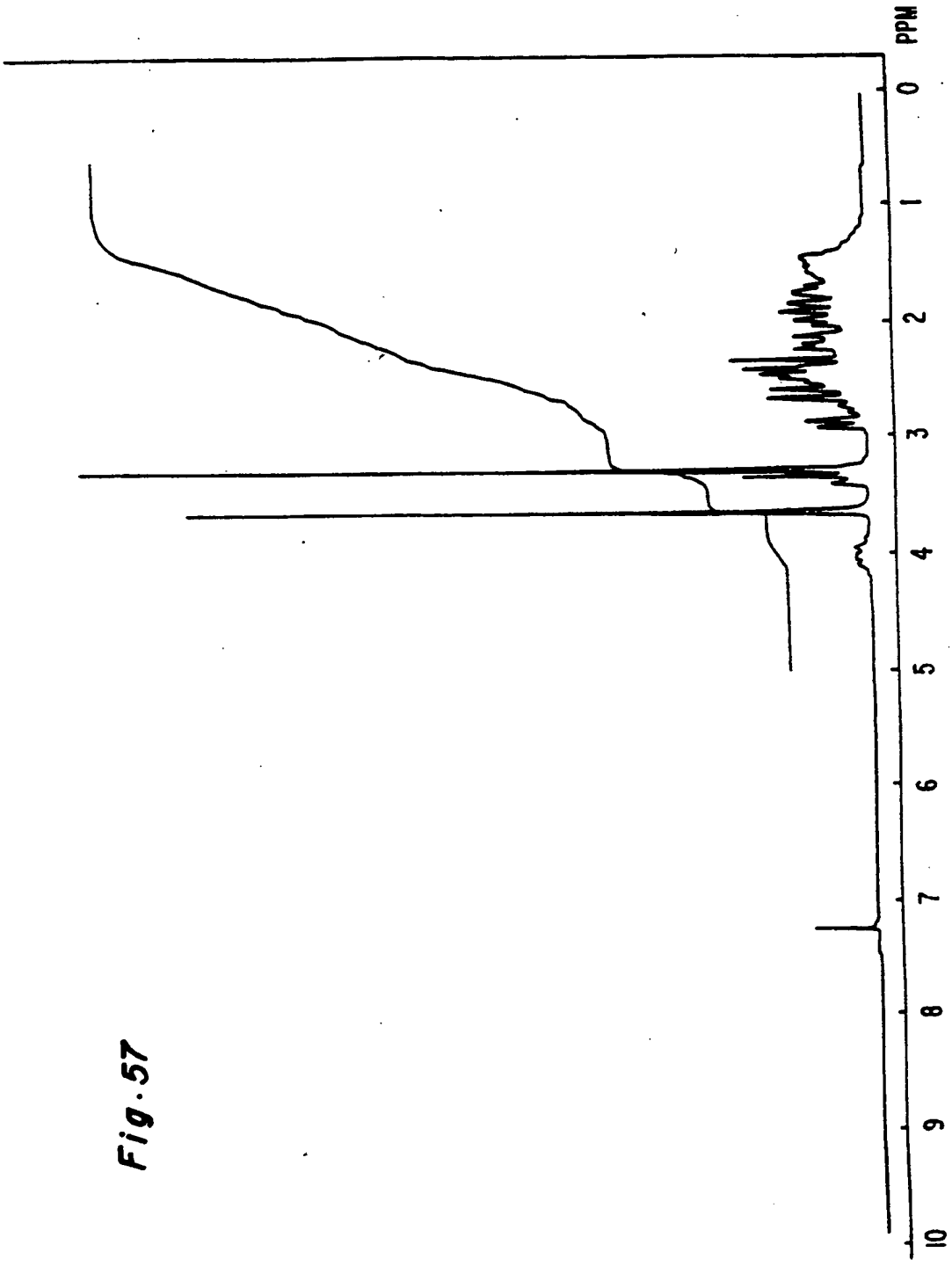


Fig. 57

PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME

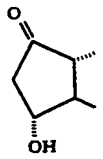
This is a divisional of application Ser. No. 07/700,895 filed May 13, 1991, now U.S. Pat. No. 5,166,174, which is a continuation of application Ser. No. 07/406,830 filed Sep. 12, 1989, abandoned, which is a continuation-in-part of application Ser. No. 07/149,445 filed Jan. 28, 1988, abandoned.

BACKGROUND OF THE INVENTION

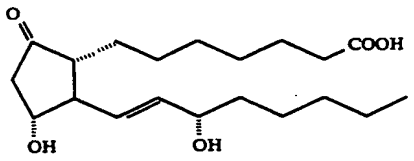
The present invention relates to a novel type of prostaglandin E and ulcer preventive agents containing the same.

Prostaglandin is a generic term for various prostanoic acids and is classified into various groups, such as E, F, A, B, C, D, and H, according to the manner in which keto and/or hydroxyl groups are introduced in five-membered ring portions. Prostaglandins will stimulate the uterine muscle and, in addition, they have various physiological and pharmacological actions, such as vasodilation, inhibition of platelet aggregation, and inflammatory action.

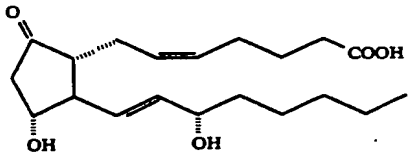
Prostaglandin E (hereinafter referred to as PGE), as a substance with a five-membered ring structure, has a group represented by:



Broadly, there are known two types of PGE, namely, PGE_1 in which the carbon-carbon bond at the 5- and 6-positions (C_5–C_6 bond) is a single bond:

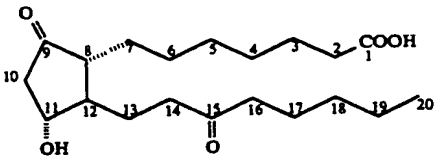


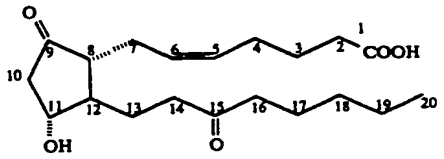
and PGE_2 in which the C_5–C_6 bond is a double bond:

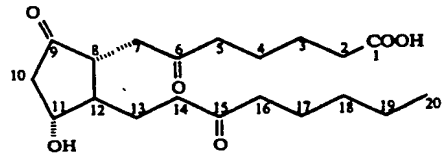


PGE_2, for example, is known as having antiulcer activity on one hand, but on the other hand it has such actions as uterine contraction, intestine contraction, and vasodilation; further it is recognized as having side effects, such as severe alvine flux. Therefore, it is unsuitable or impossible to use PGE_2 as antiulcers.

Whilst, it has been recognized that in human or animal metabolites there are present free substances similar to prostaglandin E in which C_{13}–C_{14} bond is saturated and in which the carbon at the 15-position forms a carbonyl group. These substances, or species of 13,14-dihydro-15-keto prostaglandin E are:







These corresponds to PGE_1, PGE_2, and 6-keto PGE_1 respectively, and they are known as substances which are naturally metabolically produced in vivo through enzymic metabolic reaction. These species of 13, 14-dihydro-15-keto PGE have been reported as physiologically and pharmacologically inactive metabolic products which exhibit little of the various physiological activities of PGE (Acta Physiologica Scandinavica, Vol 66, p. 509~, 1966), and has been regarded as such. Therefore, little has been expected of the pharmacological effect of these metabolic products and compounds similar to them.

SUMMARY OF THE INVENTION

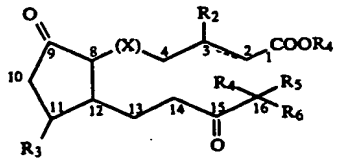
While evaluating the pharmacological activities of derivatives of the aforesaid metabolic products, the present inventor found that the derivatives, such as esters salts, one having a protective group on the carboxyl group as well as one having free carboxyl group, one having substituent groups at the 16-, 17-, 19-, and-/or 20-positions, one in which the carbon at the 11-position has a methyl group or a hydroxymethyl group, and one having an alkoxy group at the terminal of a ω chain, exhibited antiulcer activities, and that they showed no trace or a significantly reduced degree of such central and peripheral physiological effects as were simultaneously appeared as a side effect and were inherent to known or common PGE which had been recognized as having antiulcer activities.

BRIEF DESCRIPTION OF DRAWING

FIG. 1-57 show n.m.r. spectra of the prostagrandins obtained in the present invention.

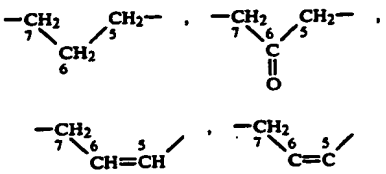
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to 13,14-dihydro-15-keto prostaglandins E represented by the general formula:



(I)

(in which
X represents:



R_1 represents: hydrogen atom, physiologically acceptable salts, physiologically acceptable protective group C_1–C_4 alkyl, benzyl, hydroxyalkyl, or alkoxyalkyl group;

R_2 represents: hydrogen atom or a methyl group;

R_3 represents: a hydroxyl, methyl, or hydroxymethyl group;

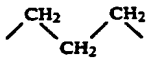
R_4 and R_5, each represents: hydrogen atom, or a methyl, hydroxyl group, or halogen atom (provided that R_4 and R_5 may be identical with or different from each other); and

R_6 represents: C_1–C_9 alkyl group which may have a branch or a double bond, or C_1–C_9 alkyl group having an alkoxy-substituent group,

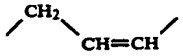
in which C_2–C_3 bond may be a double bond)
and antiulcers containing the same.

In the general formula (I), (X)- has any of the above shown structures.

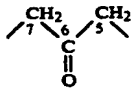
A compound where -(X)- is



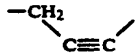
is a prostaglandin belonging to the PGE_1 group, and a compound where -(X)- is



is a prostaglandin to the PGE_2. Therefore, a compound where -(X)- is



is a prostaglandin to the 6-keto PGE_1.



is a prostaglandins E belonging to 5,6-dehydro-PGE_2.

R_1 in the general formula (I) represents hydrogen atom an alkyl, benzyl, hydroxyalkyl, alkoxyalkyl group having 1–4 carbon atoms, a physiologically acceptable salt residue, or a physiologically acceptable protective group.

The alkyl group may be a cycloalkyl group, e.g., a cyclopropyl group, a cyclopentyl group, or an alkyl group having a side chain or a double bond structure, such as, for example, isopropyl group, tert-butyl group, or allyl group. Preferably, however, it is a straight chain saturated alkyl group, or more specifically a methyl or ethyl group. Examples of the hydroxyalkyl group are hydroxyethyl and hydroxyisopropyl groups. Or, it may be an alkoxyalkyl group, such as methoxyethyl group or alkoxyalkyl group.

R_2 represents hydrogen or a methyl group, in which the carbons at the 2- and 3-positions may have a double bond.

The carboxyl group may be free, a salt residue, or a protective group. As the salt may be a physiologically acceptable salt, for example, alkaline metal salt such as sodium salt, potassium salt and the like; alkaline earth metal salt such as calcium, magnesium salt; ammonium salt; a physiologically acceptable amine salt such as salt of methylamine, dimethylamin, cyclopentylamine, benzylamine, pyperidine, monoethanolamine, diethanolamine, monomethylmonoethanolamine, tromethamine, lysine, tetraalkylammonium and the like. The protective group may include alkylsilicon such as trimethylsilicon, triethylsilicon and the like; tetrahydroxypyran and the like.

R_3 represents a hydroxyl, methyl, or ethyl group, in which the steric configuration relating to the carbon at the 11-position may take the form of α, β, or a mixture thereof. Especially, one in which such steric configuration takes the α-position.

R_4 and R_5 are independently hydrogen, methyl or hydroxyl groups, or halogens. R_4 and R_5 may be identical or different, but preferably at least one of them is a methyl group or a halogen, or more particularly fluorine atom.

R_6 is a saturated or unsaturated $C_1 \sim C_9$ alkyl group, or a $C_1 \sim C_9$ alkyl group having an alkoxy-substituent group. For the alkyl group, one having $C_4 \sim C_9$ is particularly preferred. For such $C_4 \sim C_9$ alkyl group, a straight-chain alkyl group or an alkyl group having one methyl group branch is particularly preferred. In the alkyl group having an alkoxy substituent, the alkoxy group is preferably methoxy or ethoxy, and for the alkyl group, one having $C_2 \sim C_6$ is suitable.

The prostaglandin Es of the present invention includes isomers of the aforementioned compounds. Examples of these isomers include tautomeric isomer between the hydroxyl group at 11-position and the carbonyl group of 15-position, i.e. a hemiacetal. Such a tautomeric isomer is easily formed in a compound having an electron attractive group such as a fluorine atom.

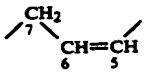
Typical examples of the compounds according to the invention are:

13,14-dihydro-15-keto-PGE_2 alkyl ester;
13,14-dihydro-15-keto-PGE_2 cycloalkyl ester;
13,14-dihydro-15-keto-PGE_2 hydroxy alkyl ester;
13,14-dihydro-15-keto-PGE_2 benzyl ester;
13,14-dihydro-15-keto-PGE_1 alkyl ester;
13,14-dihydro-6,15-diketo-PGE_1 alkyl ester;
13,14-dihydro-15-keto-18-methoxy-19, 20-dinor-PGE_2 or alkylester;
13,14-dihydro-15-keto-18-methoxy-PGE_2 or alkylester;
13,14-dihydro-15-keto-Δ^2-PGE_2 or alkyl ester;

13,14-dihydro-15-keto-20-methoxy-Δ^2-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-3R,S-methyl-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-3R,S-methyl-20-methoxy-PGE_2 or alkyl ester;
13, 14-dihydro-15-keto-11-dehydroxy-11R-methyl-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-16R,S-fluoro-11-dehydroxy-11R-methyl-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-16R,S-hydroxy-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-16R,S-fluoro-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-16R,S-methyl-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-16,16-dimethyl-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-16,16-dimethyl-20-methoxy-PGE_2or alkyl ester;
13,14-dihydro-15-keto-17S-methyl-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-19-methy-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-20-isopropropylidene PGE_2 or alkyl ester;
13,14-dihydro-15-keto-20-ethyl-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-20-ethyl-11-dehydroxy-11R-methyl-PGE2 or alkyl ester;
13,14-dihydro-15-keto-20-n-propyl-PGE_2 or alkyl ester;
13,14-dihydro-15-keto-20-ethyl-PGE_1 or alkyl ester;
13,14-dihydro-6,15-diketo-16R,S-fluoro-PGE_1 or alkyl ester;
13,14-dihydro-6,15-diketo-16R,S-fluoro-11-dehydroxy-11R-methyl-PGE_1 or alkyl ester;
13,14-dihydro-6,15-diketo-16R,S-methyl-PGE_1 or alkyl ester;
13,14-dihydro-6,15-diketo-16,16-dimethyl-PGE_1 or alkyl ester;
13,14-dihydro-6,15-diketo-19-methyl-PGE_1 or alkyl ester;
13,14-dihydro-6,15-diketo-20-methyl-PGE_1 or alkyl ester;
13,14-dihydro-6,15-diketo-11-dehydroxy-11R-methyl-PGE_1 or alkyl ester; and
13, 14-dihydro-6,15-diketo-11-dehydroxy-11R-hydroxymethyl PGE_1 alkyl ester.
13,14-dihydro-15-keto-20-methyl-PGE_1 or alkyl ester;
13,14-dihydro-15-keto-Δ^2-PGE_1 or alkyl ester
13,14-dihydro-15-keto-16R,S-fluoro-20-methyl-PGE_2 or alkyl ester,
13,14-dihydro-15-keto-16,16-difluoro-PGE_2 or alkyl ester,
13,14-dihydro-15-keto-5,6-dehydro-20-methoxy-PGE_2 or alkyl ester.

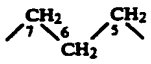
The prostaglandins E of the present invention can be synthesized in such way as shown illustrated in examples and the accompanying synthesis charts (I)~(XXI). That is, a commercially available (−) or (±) Corey lactone (1) may be used as the starting material, and then collins-oxidized to give an aldehyde (2); the aldehyde (2) may be reacted with dimethyl (2-oxoalkyl) phosphonate to give an α, β-unsaturated ketone (3), which is then reducted. The resulting unsaturated ketone (4) is protected with respect to its carbonyl group. A hydroxyl group after protective group, p-phenylbenzoate being removed is protected with THP. After lactone (7) is reduced to lactol (8), an α chain is introduced by Wittig reaction.

The PGE_2 in which - (X) - is



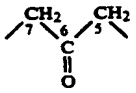
can be obtained by reducing the lactone (7) to lactol (8), then subjecting the lactol (8) to reaction with (4-carboxybutyl) triphenylphosphonium bromide.

The PGE_1 in which - (X)- is

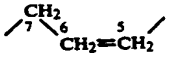


can be obtained through reduction of the PGE_2.

The 6-keto PGE_1 in which - (X)- is

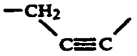


can be obtained by adding bromine or iodine atom on C_5–C_6 double bond of

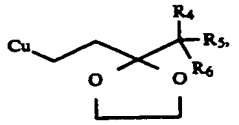


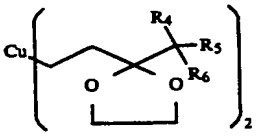
using N-bromosuccinimide or iodine atom, and simultaneously cyclizing the C_6-carbon and the hydroxyl group at the 9-position to give a bromide or a iodide, and then the bromide or iodide is treated with DBU to ketonize the carbon at the 6-position.

5,6-Dehydro-PGE_2s in which (X) is:



may be prepared by treating copper enolate which can be prepared by adding a monoalkyl-copper complex or a dialkylcopper complex of following formula on 1,4-position of 4R-t-butyldimethylsilyloxy-2-cyclopentene-1-on (167):





with 6-carboalkoxy-1-iodo-2-hexine or its derivatives.

The compound in which R_3 is a methyl group can be obtained by Jones- oxidizing the hydroxyl group at the 9-position in 11-tosylate to form an PGA-type, then subjecting it to the action of a dimethyl copper complex. Alternatively, the compound can be synthesized by protecting the carbonyl group of the saturated ketone (4) obtained by reduction of the unsaturated ketone (3), turning into tosylate the alcohol obtained after re-

lease of P-phenylbenzoyl group, treating the tosylate with DBU, turning the resulting unsaturated lactone into lactol, introducing an α-chain into the lactol through Wittig reaction, oxidizing the resulting alcohol (9-position) to form an PGA-type, to which a dimethyl copper complex is reacted, then introducing a methyl group into the 11-position.

The compound in which R_3 is hydroxymethyl group can be obtained by applying benzophenone as a photosensitizer to the A-type prostaglandin (PGA) obtained in manner as above described, then adding methanol.

For the synthesis of the PGE in which either R_4 or R_5 is a group other than hydrogen atom, and of the PGE in which R_6 is other than n-butyl, the compound used in obtaining the α, β-unsaturated ketone (3), namely, dimethyl (2-oxoalkyl) phosphonate should be correspondingly replaced by other suitable compound. For example, where R_4 is fluorine atom, R_6 is n-butyl, and R_5 is hydrogen atom, dimethyl (3-fluoro-2-oxopeptyl) phosphonate may be used. Where R_4 and R_5 are hydrogen atom, and R_6 is an isopentyl group, dimethyl (6-methyl-2-oxoheptyl) phosphonate may be used.

The synthesis of the compounds of the invention is not limited to the foregoing. For protection of individual functional groups and for oxidation-reduction, suitable procedures may be applied as required.

The prostaglandins E of the present invention may be used as medicines for animal and human. Usually, they are used systemically or locally in various ways, such as oral administration, intravenous injection, and subcutaneous injection. The dosage varies according to the subject for administration, animal or human, age, weight, symptoms, efficacy of treatment, method of administration, and time of treatment.

Where the compounds of the invention are used in the form of solid compositions for oral administration, they include tablets, powder, and granules. In such solid composition, one or more active substances are mixed with at least one kind of inactive diluent, for example, lactose, mannitol, grape sugar, hydroxypropyl cellulose, crystallite cellulose, starch, polycinyl pyrrolidone, or magnesium metasilicoaluminate. Such composition may, according to the conventional procedure, contain some additive other than said inactive diluent, e.g., lubricant, such as magnesium stearate, decomposer, such as calcium fibrogluconate, etherified cyclodextrin, such as a, α, β- or γ-cyclodextrin, dimethyl-α-, dimethyl-β-, or hydroxypropyl-β-cyclodextrin, branched cyclodextrin, such as glucosyl-, or maltosylcyclodextrin, or stabilizer, such as formylated cyclodextrin, sulfur-containing cyclodextrin, misoprotol, or phospholipid. The aforesaid cyclodextrins may provide increased stability. The stability may be improve by forming liposome with a phospholipid.

Tablets or pills may be coated or covered with a gastrically soluble material, such as refined sugar, gelatin, hydroxypropyl cellulose, or hydroxypropyl methyl cellulose phthalate, or a film of such matereial in one or more layers. Also, they may be encapsulized with an absorbable material, such as gelatin.

In the form of liquid compositions for oral administration, the compounds of the invention include medically allowable emulsions, solutions, suspensions, syrups, and elixers. They may contain inactive diluents conventionally used, such as, for example, refined water, ethanol, and coconut oil. In addition to such inactive diluent, the compositions may contain wetting agents, auxiliary agents, such as suspensions, edulcorants, flavors, aromatics, and preservatives. The liquid compositions may be encapsulated as such in soft capsules and the like.

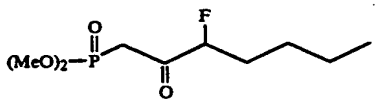
Other forms of compositions for oral administration include sprays prepared per se according to the usual known procedures which may contain one or more kinds of active substances.

The compounds of the invention in the form of injections for non-oral administration include sterile aqueous and non-aqueous solvents, suspensions, emulsions, and detergents.

The aqueous solutions and suspensions include, for example, distilled water and physiologic salt solution. The non- aqueous solutions and suspensions include, for example, vegetable oils, such as polyethylene glycol and olive oil, alcohols, such as ethanol, and Polysorbate. Such composition may contain auxiliaries, such as presevatives, wetting agents, emulsions, and dispersions. These compositions are sterilized by being passed through bacteria retaining filters or by incorporation of bactericides, or by light irradiation. It is also possible to first prepare a germ-free solid composition and dissolve same in a germ-free injection solvent before using it as an injection.

EXAMPLE 1

1) Preparation of Dimethyl (3R,S-Fluoro-z-oxoheptyl)phosphonate



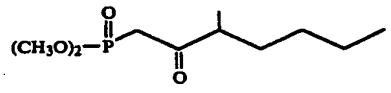
1 - 1 Methyl 2-R,S-Fluorocaproate:

Methyl 2R,S-bromocaproate (40 g) was added to anhydrous potassium fluoride (23 g) in acetoamide (23 g) kept at 105° C. The mixture was vigorously stirred at 105° C. for 6h. A crude product obtained after the usual work-up, was distilled under reduced pressure. Yield 20 g (71%), b.p. 66° C./20 mmHg.

1 - 2 Dimethyl (3R,S-Fluoro-2-oxoheptyl) phosphonate:

Dimethyl methylphosphonate (8.38 g) was dissolved in dry THF (200 ml), and the resulting solution was cooled to −78° C. n-Butyl lithium (1.6-M, 42 ml) was added dropwise to the solution, and 10 min later 10 ml of the THF solution of methyl 2R, S-fluorocaproate (20 g) was added dropwise. After the addition, the reaction solution was stirred at −78° C. for 45 min, and then at room temperature for 45 min. A crude product obtained after the usual work-up was chromatographed (hexane: ethyl acetate=1:1). Yield 5.04 g (62%).

2) Preparation of Dimethyl (3R,S-Methyl-2-oxoheptyl)phosphonate



2 - 1 Methyl 2R,S-Methylcaproate:

A THF (50 ml) solution of dissopropylamine (12.9 ml) was cooled to −78° C. and n-BuLi (1.6-M, 57,6 ml) was added dropwise over 1.5 h (preparation of LDA). A solution of methyl caproate (10 g) in THE (50 ml)

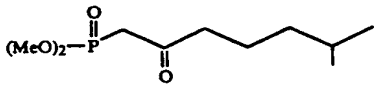
was added dropwise to the prepared LDA over 50 min. After stirring for 2 h, a solution of methyl iodide (6.2 ml) in THF (20 ml) was added dropwise over 40 min. The reaction solution was stirred at −78° C. for 1 h, and then at room temperature overnight.

After the usual work-up, the resulting residue was distilled under reduced pressure, and thus 3.15 g of methyl 2R,S-methylcaproate (b.p. 44° C./10 mmHg) was obtained.

2 - 2 Dimethyl (3-Methyl-2-oxoheptyl)phosphonate:

To a THF (120 ml) solution of dimethyl methylphosphonate (5.04 g) at −60° C. was added dropwise n-BuLi (1.6-M, 25.4 ml), and the mixture was stirred for 30 min. A THF (50 ml) solution of methyl 2R,S-methylcaproate (3.15 g) was added dropwise. The mixture was stirred at −60° C. for 1 h, then at room temperature for 1.5 h, and thereafter acetic acid (2 ml) was added at 0° C. A crude product obtained after the usual work-up was chromatographed (hexane: ethyl acetate=1:5). Yeild: 2,85 g (58%).

3) Preparation of Dimethyl (6-Methyl-2-oxoheptyl)phosphonate



3 - 1 Methyl 5-methylcaproate:

Sodium ethoxide was prepared from sodium metal (9.1 g) and freshly distilled absolute ethanol (250 ml). Diethyl malonate (63.5 g) was added to sodium ethoxide in ethanol, and the mixture was stirred at 60°–70° C. for 50 min. Isoamyl bromide (60 g) was added, and the reaction mixture was heated under reflux overnight. After the usual work-up, the resulting crude product was distilled under reduced pressure to give diethyl isoamylmalonate. Yield: 71.7 g (78%).

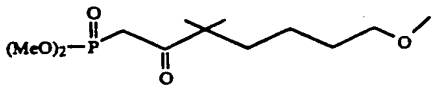
Diethyl isoamylmalonate (71.7 g) was added to a 50% aqueous solution of sodium hydroxide (60 ml), and the mixture was heated under reflux for 6 h. After cooling, the mixture was extracted with ether; the water layer was acidified with hydrochloric acid and, after saturation with sodium chloride, was extracted with ether. The extracts from the acidic aqueous layer were concentrated under reduced pressure to give isoamylmalonic acid. The obtained dicaboxylic acid was heated at 180° C. for 2 h. After distillation under reduced pressure, 5-mehyl-caproic acid was obtained. Yield: 30 g (75%), b.p. 107°–108° C./11 mmHg.

The 5-methyl-caproic acid (30 g) was treated with methanol (600 ml) and sulfuric acid (3 ml), and thus methyl 5-methylcaproate was obtained. Yield: 27 g (81%).

3 - 2 Dimethyl (6-Methyl-2-oxoheptyl)phosphonate:

Dimethyl (6-methyl-2-oxoheptyl)phosphonate was prepared from methyl 5-methylcaproate and dimethyl methylphosphonate according to the known method.

4) Preparation of Dimethyl (3,3-Dimethyl-7-methoxy-2-oxoheptyl)phosphonate



4 - 1 Methyl 2,2-Dimethyl-6-methoxy caproate:

1,4-Butanediol (50 g) was treated with sodium hydride (NaH) (60%, 26,6 g) and methyl iodide (250 g) in THF (150 ml) to give 4-methoxy-1-butanol. Yield: 21.8 g (38%), b.p. 135/760 mmHg.

4-Methoxyl-1-butanol (8.49 g) was treated with p-toluenesulfonyl chloride and 4-dimethylaminopyridine in methylene chloride (150 ml) to give 4-methoxy-butyl-1-tosylate. Yield: 16.1 g (77%).

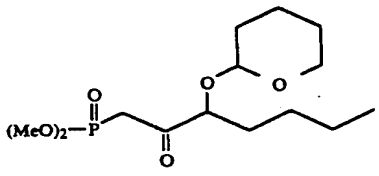
4-Methoxy-butyl-1-tosylate (16.1 g), together with NaI (18.7 g), was agitated in acetone (80 ml) at room temperature for 3 h to give 1-iodo-4-methoxy-butane (9.05 g, 68%).

To N-isopropylcyclohexylamine (5.96 ml) in THF (30 ml) was added dropwise n-BuLi (1,6-M, 22.7 ml) at −78° C., and the mixture was stirred for 30 min, to which a THF (5 ml) solution of methyl isobutyrate (3.43 g) was added, and stirred at −78° C. for 45 min. Then, a HMPA (6.3 ml) solution of 1-iodo-4-methoxy-butane (9.05 g) was added to the mixture, and stirred at room temperature for 1 h to give methyl 2,2-dimethyl-6-methoxycaproate (4.81 g, 85%) after usual work-up.

4 - 2 Dimethyl (3,3-Dimethyl-7-methoxy-2-oxoheptyl)phosphonate:

Prepared from methyl 2,2-dimethyl-6-methoxycaproate and dimethyl methylphosphonate according to the known method.

5) Preparation of Dimethyl (3-(2-Tetrahydropyranyl)oxy-2-oxoheptyl)phosphonate



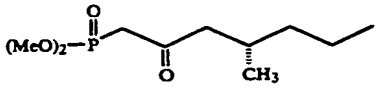
5 - 1 Methyl 2-(2-Tetrahydropyranyl)oxycaproate:

A tetrahydropyranyl ether was prepared from commercially available methyl 2R,S-hydroxycaproate according to the usual method. (Yield 71%).

5 - 2 Dimethyl (3-(2-Tetrahydropyranyl)oxy-2-oxoheplyl)phosphonate:

Prepared from methyl 2-(2-tetrahydropyranyl) oxycaproate and dimethyl methylphosphonate according to the known method. (Yield 48%).

6) Preparation of Dimethyl(4S-methyl-2-oxoheptyl)phosphonate



6 - 1 Ethyl 3S-Methyl-caproate:

Sodium ethoxide was prepared from sodium metal (7.61 g) and absolute ethanol (200 ml). Diethyl malonate (50.3 ml) was added dropwise to the ethanol containing sodium ethoxide. After heating to 80° C., 2-bromopentane (50 g) was added and the mixture was reflued for 24 h. Diethyl (2-pentyl)malonate (62.7 g) was obtained after the usual work-up. Diethyl (2-pentyl)malonate was added to a 50% potassium hydroxide solution and the mixture was heated for 3 h while water/ethanol

being distilled off. After cooling, the solution was acidified with concentrated hydrochloric acid. Then, the solution was extracted with ethyl acetate. The extract was concentrated under reduced pressure, and the resulting product was heated to 180° C. until bubbling ceased. After distillation, colorless 3R,S-methy-caproic acid was obtained. Yield: 27.7 g (35%), b.p. 200° C./760 mmHg.

3R,S-Methyl-caproic acid was dissolved in ehanol (160 ml) and cinchonidine (64 g) was added and dissolved under heating.

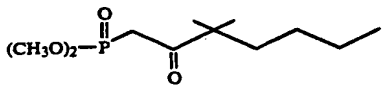
The solution was concentrated under reduced pressure, and the resulting salt was recrystallized from 60% methanol six times to give needle crystals. Yield: 14.4 g, $(\alpha)_D^- = -3.3$ (C=13.6 (benzene) literature value −3.1)

3S-Methyl-caproic acid (3.94 g) was converted to the corresponding ethyl ester with using ethanol and catalytic amount of sulfuric acid. Yield: 4.04 g (84%).

6 - 2 Dimethyl(4S-Methyl-2-oxoheptyl)phosphonate:

This compound was prepared from ethyl 3S-methyl-caproate and dimethyl methylphosphonate according to the known method.

7) Preparation of Dimethyl (3,3-Dimethyl-2oxoheptyl)phosphonate



7 - 1 Ethyl 2,2-Dimethyl-caproate:

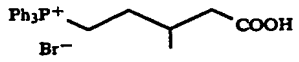
To LDA prepared at −78° C. in the usual manner was added ethyl isobutyrate (45 g) in THF, and stirred for 1 h. A dry HMPA solution of butyl iodide (107 g) was added, and the mixture was stirred at −78° C. for 1 h and then at room temperature for additional 1 h.

A crude product obtained after tile usual work-up was distilled. Yield: 50 g (75%), b.p. 68° C./25 mmHg.

7 - 2 Dimethyl(3,3-Dimethyl-2-oxoheptyl) phosphonate:

Prepared from ethyl 2,2-dimethyl-caproate and dimethyl methylphosphonate according to the usual method.

8) Preparation of (3R,S-Methyl-4-carboxybutyl) triphenylphosphonium bromide



In ether (300 ml), 3-methyl-1,5-pentanediol (23.3 g) was converted to 5-acetoxy-3-methyl-1-pentanol with pyridine (16 ml) and acetyl chloride (14 ml) at 0° C. Yield: 18.4 g.

5-Acetoxy-3-methyl-l-pentanol was oxidized with Jones reagent in acetone (200 ml) at −20° C. to give 5-acetoxy-3R,S-methyl valeric acid. Yield: 8.2 g (24%).

To 5-acetoxy-3R,S-methyl valeric acid (8.2 g) was added hydrobromic acid (40 ml) and concentrated sulfuric acid (10 ml), and the mixture was agitated at 90° C. overnight. Thereafter, the solution was poured into iced water. A crude product obtained after the usual work-up was chromatographed (ethyl acetate: hexane=1.5), and thus 8.0 g of 5-bromo-3R,S-methyl valeric acid (87%) was obtained.

5-Bromo-3R,S-methyl valeric acid with triphenyl phosphine (21.5 g) was reflued in acetonitrile (100 ml) for 2 days. The reaction solution was poured into ether and the resulting precepitate was separated by filtration. Thus, (3-R,S-methyl-4-carboxybutyl)triphenylphosphonium bromide was obtained. Yield: 9.78 g (52%).

EXAMPLE 2 (SEE CHART I)

Preparation of 13,14-Dihydro-6,15-diketo-PGE_1 ethyl ester (15), R: Et

2 - 1 Preparation of 1S-2-Oxa-3-oxo-6R-(3-oxo-1-trans-octenyl)-7R-(4-phenylbenzoyl)oxy-cis-bicychlo(3, 3, 0) octane (3):

To the suspension of sodium hydride (NaH) (60%, 250 mg) in THF (40 ml) was added dropwise dimethyl(2-oxoheptyl)phosphonate, and the reaction solution was stirred for 30 min. A THF solution (40 ml) of the aldehyde (2) previously prepared by Collins oxidization of (−)-Corey lactone (1) (2 g) was added. Reaction was maintained at room temperature overnight, and then acetic acid was added. After the usual work-up, an α,β-unsaturated ketone (3) was obtained. Yield: 1.95 g (50%).

2 - 2 Preparation of 1S-2-Oxa-3-oxo-6R-(3,3-ethylenedioxyoctanyl)-7R-(4-phenylbenzoyl)oxy-cis-bicyclo (3,3,0) octane (5):

The unsaturated ketone (3) was hydrogenated in ethyl acetate (100 ml) with using 5% paradium-carbon (100 mg) and hydrogen to give the corresponding saturated ketone (4).

The ketone (4) (1.95 g) was dissolved in toluene (150 ml), and ethylene glycol and p-toluenesulfonic acid (catalytic amount) were added. The solution was heated under reflux overnight while water produced was distilled off. After the usual work-up, ketal (5) was obtained. Yield: 1.8 g (84%).

2 - 3 Preparation of 1S-2-Oxa-3-oxo-6R-(3,3-ethylenedioxy-1-octanyl)-7R-hydroxy-cis-bicyclo (3,3,0) octane (6):

The compound (5) (1.8 g) was dissolved in methanol (80 ml) and THF (20 ml), and after addition of potassium carbonate (0.563 g), the solution was stirred at room temperature for 7 h. A crude product obtained by a usual manner was chromatographed (ethyl acetate-hexane=1:3→1:1) to give alcohol (6). Yield: 0.95 g (82%).

2 - 4 Preparation of tetrahydropyranyl ether (7):

The compound (6) (0.95 g) was dissolved in dichloromethane (100 ml) and then dihydropyran (0.76 g) and p-toluene sulfonate (catalytic amount) were added. The resulting solution was stirred overnight. After the usual work-up and purification, tetrahydropyranyl ether (7) was obtained. Yield: 1.06 g (88%).

2 - 5 Preparation of lactol (8):

To the tetrahydropyranyl ether (7) (1.06 g) in dry toluene (30 ml) at −78° C. was added dropwise diisobutylaluminum hydride (DIBAL-H) (1.5M, 2.3 ml) and stirred for 60 min. Lactol (8) was obtained after the usual work-up.

2 - 6 Preparation of 13,14-Dihydro-11-(2-tetrahydropyranyl)oxy-15,15-ethylenedioxy $PGF_{2\alpha}$(9):

Sodium hydride (60%, 0.86 g), washed with pentane, was suspended in DMSO (50 ml), and stirred for 90 min at 60°~70° C. After the reaction solution was cooled to room temperature, (4-carboxybutyl)triphenylphosphonium bromide in DMSO was added, and agitated for 30 min, to which lactol (8) in DMSO (10 ml) was added. After stirred overnight, the reaction solution was poured into ice-water, made basic with addition of

20% sodium hydroxide solution, and extracted with ether. The aqueous layer was adjusted to pH 4~5 with 4N-hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with water, then with saturated sodium chloride solution, and was dried over magnesium sulfate. Thereafter, the solvent was distilled off. Ether was added and insolubles were separated by filtration. The filtrate was concentrated under reduced pressure to give the compound (9).

2 - 7 Esterification of the compound (9);

Preparation of the compound (10), R=Et:

The carboxylic acid (9) was dissolved in dry acetonitrile (50 ml) and then DBU (0.48 g) and ethyl iodide (1.76 g) were added. The solution was stirred at room temperature overnight. A crude product was obtained after the usual work-up, and was column-chromatographed (ethyl acetate-hexane 1:3). Thus, 1.04 g of ethylester (10) was obtained. (Yield: 76% from (7))

2 - 8 Preparation of the compound (11):

The alcohol (10) (1.04 g) was dissolved in dry tetrahydrofuran (3.4 ml) and dry methylene chloride (26.4 ml), and after addition of NBS (0.364 g) at 0° C., the reaction solution was stirred for 5 min. A crude product was obtained after the usual work-up, and chromatographed (ethyl acetate-hexane=1:3) to give the compound (11). Yield: 0.61 g (51%).

2 - 9 Preparation of 13,14-Dihydro-15,15-ethylenedioxy-6-keto-11-(2-tetrahydropyranyl)oxy-$PGF_{1\alpha}$ ethyl ester (13):

The bromoether (11) (0.61 g) was dissolved in dry toluene (30 ml), and then DBU (25 ml) was added. The solution was agitated at 40° C. overnight. After the end of the period, the solution was cooled with ice and 1N-hydrochloric acid was added to acidify the solution, and agitated for 10 minutes. Subsequently, the solution was extracted with ethyl acetate. A crude product was obtained after the usual work-up, and then chromatographed (ethyl acetate-hexane=1:3→1:1) to give the compound (13). Yield: 0.332 g (61%).

2 - 10 Preparation of 13,14-Dihydro-15,15-ethylenedioxy-6-keto-11-(2-tetrapyranyl)oxy-PGE_1 ethyl ester (14):

The alcohol (13) (0.332 g) was oxidized in acetone (20 ml) at −20° C. with Jones reagent (2.67M, 0.36 ml). A crude product obtained after the usual work-up was chromatographed (ethyl acetate-hexane=1:3) to give the compound (14). Yield: 0.198 g (58%).

2 - 11 Preparation of 13,14-Dihydro-6,15-diketo-PGE_1 ethyl ester (15):

The tetrahydropyranyl ether (14) (0.198 g) was dissolved in a mixed solvent (14 ml) of acetic acid: water: THF (4:2:1), and the solution was stirred for 1 h at 45° C. Benzene was added, and the solvent was removed under reduced pressure. The resulting crude product was chromatographed (ethyl acetate-hexane=1:3) to give 13,14-dihydro-6,15-diketo-PGE_1 ethyl ester (15). Yield: 0.098 g (65%).

The n. m. r. spectrum of 13,14-dihydro-6,15-diketo-PGE_1ethyl ester (15) is shown in FIG. 1.

Mass (SIMS) m/z: 397 $(M+H)^+$, 379 $((M+H)^+-18)$, 287, 157, 111, 99.

EXAMPLE 3 (SEE CHART I)

Preparation of (±) 13,14-Dihydro-6,15-diketo-PGE_1 ethyl ester (15), R: Et

Preparation of the title compound was carried out using (±)-Corey lactone (1) and a similar manner to the Example 1.

The n. m. r. spectrum of (±)-13,14-dihydro-6,15-diketo-PGE_1 ethyl ester (15) is shown in FIG. 2.

Mass (SIMS) m/z: 397 $(M+H)^+$, 379 $((M+H)^+-18)$, 287, 157, 111, 99.

EXAMPLE 4 (SEE CHART I)

Preparation of 13,14-Dihydro-6,15-diketo-PGE_1 methyl ester (15), R: Me

Preparation of the title compound was carried out in the same way as in Examples 2 and 3, except that (−)-Corey lactone (1) was used, and that the carboxylic acid (9) was methylated with diazomethane to give the compound (10) ($R=CH_3$).

The n. m. r. spectrum of the 13,14-dihydro- 6,15-diketo-PGE_1 methyl ester (15) is shown in FIG. 2.

Mass (SIMS) m/z: 405 $(M+H)^+$, 383 $((M+H)^+-18)$, 365, 287, 143, 121, 111, 99.

EXAMPLE 5 (SEE CHARTS I and II)

Preparation of 13,14-Dihydro-15-keto-3R,S-methyl-PGE_2 methyl ester (19)

Sodium hydride (60%, 1.72 g), washed with pentane, was suspended in dry DMSO, and the suspension was agitated for 45 min at 70° C. After the reaction solution was ice-cooled, a DMSO solution of (3R,S-methyl-4-carboxybutyl)triphenylphosphonium bromide was added. The reaction was stood at room temperature. Then, a DMSO solution of lactol (8) produced from (−)-Corey lactone with the procedure shown in Examples 2 to 4 was added, and agitated for 2 h. The resultant was diluted with a mixed solvent of ether and ethyl acetate (1:1), and poured into 5% potassium carbonate solution. After vigorous stirring, separated organic layer was extracted with aqueous potassium carbonate solution twice. The combined basic aqueous layers were acidified with hydrochloric acid at 0° C., and then were extracted with ethyl acetate three times. The combined ethyl acetate layers were washed with sodium chloride solution, and then concentrated under reduce pressure. The residue thus obtained was dissolved in ether and insolubles were filtered off. The filtrate was partially concentrated and was treated with diazomethane. After subseqent concentration, a crude product was obtained, and was chromatographed (ethyl acetate-hexane=2:5) to give a colorless oily substance (17) (2.15 g, 56%).

The alcoholic substance (17) (2.1 g) was oxidized in acetone (60 ml) at −30° C. with Jones reagent (2.67-M) (2.20 ml).

A residue obtained after the usual work-up was chromatographed (ethyl acetate: hexane=1:3) to give a colorless oily substance (18) (1.64 g, 77%).

The tetrahydropyranyl ether (18) (1.64 g) was dissolved into a mixed solvent (50 ml) of acetic acid: water: THF (4:2:1), and agitated for 3 h at 45° C. The reaction solution was concentrated under reduced pressure, and the resulting crude product was chromatographed (ethyl acetate: benzene=4:5) to give a colorless oily

substance, 13,14-dihydro-15-keto-3R,S-methyl-PGE_2 methyl ester (19). Yield: 0.98 g (80%).

The n. m. r. spectrum of 13,14-dihydro-15-keto-3R,S-methyl-PGE_2 methyl ester (19) is shown in FIG. 3.

Mass (D I) m/z: 380 (M^+), 362 (M^+- 18), 208, 109, 94, 81.

EXAMPLE 6 (SEE CHART III)

Preparation of 13,14-Dihydro-15-keto-16R,S-methyl-PGE_2ethyl ester (29), R=Et

6 - 1 Preparation of 1S-2-Oxa-3-oxo-6R-(4R,S-methyl-3-oxo-1-trans-octenyl)-7R-(4-phenyl) benzoyloxy-cis-bicyclo (3, 3, 0) octane (20):

Sodium hydride (60%, 0.228 g) was suspended in anhydrous THF (40 ml), and a THF (30 ml) solution of dimethyl (3R,S-methyl-2-oxoheptyl)phosphonate (1.4 g) was added with agitation for 30 min. To the resultant was added a THF solution (30 ml) of the aldehyde (2) obtained after collins oxidation of (−)- Corey lactone. The reaction was kept at room temperature for 2 h, and then acetic acid was added to neutralize the reaction. An α,β-unsaturated ketone (20) was obtained after the usual work-up and the purification. Yield: 1.606 g (61%).

6 - 2 Preparation of 1S-2-oxa-3-oxo-6R-(3,3-ethylenedioxy-4R,S-methyl-1-octanyl)-7R-(4-phenyl) benzoyloxy-cis-bicyclo (3, 3, 0) octane (22):

The α,β-unsaturated ketone (20) was hydrogenated in ethyl acetate with 5% palladium-carbon (0.150 g), and hydrogen. The saturated ketone (21) thus obtained was dissolved in anhydrous benzene (150 ml), to which p-toluenesulfonic acid (in catalytic amount) and ethylene glycol (10 ml) were added, and refluxed overnight while water was distilled off. Ketal (22) was obtained after the usual work-up. Yield: 1.538 g (87%).

6 - 3 Transesterification of the ketal (22): Synthesis of alcohol (23):

The ketal (22) (1.538 g) was dissolved in absolute methanol (100 ml), and K_2CO_3 (0.503 g) was added, the reaction was stirred for 5 h.

The reaction solution was neutralized with addition of acetic acid.

A crude product obtained after the usual work-up was chromatographed (ethyl acetate: hexane=1:2) to give the alcohol (23). Yield: 0.8682 g (88%).

6 - 4 Preparation of Tetrahydropyranyl ether (24):

The compound (23) (0.8682 g) was dissolved in dry CH_2Cl_2(100 ml), and dihydropyran (5 ml) and p-toluenesulfonic acid (catalytic amount) were added. The reaction solution was stirred for 20 min. A crude product obtained after the usual work-up was chromatographed (hexane: ethyl acetate=5:1) to give the tetrahydropyranyl ether (24). Yield: 1.040 g (94%).

6 - 5 Preparation of lactol (25):

The tetrahydropyranyl ether (24) was treated with DIBAL-H (1.5-M, 5 ml) in dry toluene (30 ml) at −78° C. to give the lactol (25). Yield: 1.030 g.

6 - 6 Preparation of 13,14-Dihydro-15,15-ethylenedioxy-16R,S-methyl-11-(2-tetrahydropyranyl) oxy-$PGF_{2\alpha}$ (26):

Sodium hydride (50%, 0.600 g) washed with dry ether was suspended in DMSO (8 ml), and the suspension was heated at 60° C. for 1 h with agitation. A DMSO (10 ml) solution of (4-carboxybutyl)triphenylphosphonium bromide (3.3 g) was added dropwise. Deep red ylide was obtained, to which the above lactol (25) in DMSO (8 ml) was added. The reaction was kept overnight at room temperature with stirring, and then poured into an ice-water, the aqueous solution was adjusted to pH 12 with 10% sodium hydroxide solution. The basic aqueous solution was extracted with ethyl acetate. The aqueous layer was adjusted to PH 6 with 1N hydrochloric acid at 0° C., and was extracted with ethyl acetate, and the combined organic extract were washed with brine. After drying, the extract was concentrated under reduced pressure to give the carboxylic acid (26). Yield: 1.299 g.

6 - 7 Preparation of ethyl ester (27), R=Et:

Esterification of the compound (26):

The carboxylic acid (26) (1.299 g) was dissolved in dry acetonitrile (50 ml). To the solution were added ethyl iodide (0.6 g) and DBU (0.4750 g). The mixture was kept at 60° C. for 2 h. A crude product obtained after the usual, work-up, was chromatographed (hexane: ethyl acetate=2:1) to give 0.6226 g of the ethyl ester (27). (Yield: 48%, from (24)).

6 - 8 Preparation of ketone (28):

The ethyl ester (27) (0.6226 g) was oxidized with Jones reagent (2.67 - M, 0.45 ml) in acetone (40 ml) at −40° C.

A crude product obtained after the usual work-up was chromatographed (hexane-ethyl acetate=3:1). Yield: 0.3942 g (63%).

6 - 9 Preparation of 13,14-Dihydro-15-keto-16R,S-methyl-PGE_2 ethyl ester (29): The ketone (28) (0.3942 g) was dissolved in a mixted solvent (10 ml) of acetic acid: water: THF (3:1:1), and the solution was kept at 40,° C. for 4 h. A crude product obtained after the usual work-up was chromatographed (hexane-ethyl acetate=4:1) to give 13,14-dihydro-15-keto-16R,S-methyl-PGE_2ethyl ester (29). Yield: 0.1559 g (53%).

The n. m. r. spectrum of the 13,14-Dihydro-15-keto,-16R,S-methyl-PGE_2ethyl ester (29) is shown in FIG. 4.

Mass (SIMS) m/z: 395 $(M+H)^+$, 377 $((M+H)^+-18)$, 331, 203, 109, 85.

EXAMPLE 7 (SEE CHART III)

Synthesis of 13,14-Dihydro-15-keto-16R,S-methyl-PGE_2methyl ester (29), R=Me

The title compound (29) was prepared in the same manner as in Example 6 except-that the carboxylic acid (26) was methylated with diazomethane.

The n. m. r. spectrum of the 13,14-dihydro-15-keto-16R,S-methyl-PGE_2 methyl ester (29) is shown in FIG. 5.

Mass (D I) m/z: 380 (M^+), 362 ((M^+-18)), 331, 249, 234, 222, 137, 109.

EXAMPLE 8 (SEE CHART IV)

Synthesis of 13,14-Dihydro-6,15-diketo-16R,S-methyl-PGE_1 ethyl ester (33), R=Et

8 - 1 Preparation of bromide (30) R=Et:

PGF_2-ethyl ester derivative (27) (1.405 g) was dissolved in a mixted solvent (50 ml) of THF-CH_2Cl_2 (2:5). To the solution was added a THF-CH_2Cl_2 (2:5; 20 ml) solution of NBS (0.5250 g) at 0° C., which was agitated for 20 min. A crude product obtained after the usual work-up was chromatographed (hexane: ethyl acetate=3:1) to give the bromide (30). Yield: 1.592 g (98%).

8 - 2 Preparation of 13,14-Dihydro-15,15-ethylenedioxy-6-keto-16R,S-methyl-11-(2-tetrahydropyranyl-)oxy-$PGF_{2\alpha}$ ethyl ester (31):

The bromide (30) (1.592 g) was dissolved in toluene (4 ml) and DBU (3.5 ml), and the solution was stirred at 50° C. overnight. After cooled, the solution was diluted with ether, and washed with sodium hydrogensulfite solution. A crude product obtained after the usual work-up was chromatographed (hexane: ethyl acetate=1.5:1) to give the compound (31). Yield: 1.031 g (72%).

8 - 3 Preparation of ketone (32):

The 6-keto-PGF derivative (31) (0.5012 g) was oxidized with Jones reagent (2.67-M: 1.2 ml) in acetone (35 ml) at −25° C. A crude product obtained after the usual work-up was chromatographed (hexane: ethyl acetate v=1:1) to give the ketone (32). Yield: 0.3907 g (78%).

8 - 4 Preparation of 13,14-Dihydro-6,15-diketo-16R,S-methyl-PGE_1 ethyl ester (33):

The 6-keto-PGF derivative (32) (0.3907 g) was dissolved in a mixed solvent (24 ml) of acetic acid: water: THF (3:1:1) and the solution was kept at 50° C. for 3.5 h. After cooled, the solution was concentrated under reduced pressure. The resulting crude product was chromatographed (hexane: ethyl acetate=1:1) to give 13,14-dihydro-6,15-diketo-16R,S-methyl-PGE_1 ethyl ester (33). Yield: 0.2100 g (71%).

The n. m. r. spctrum of 13,14-dihydro-6,15-diketo-16R,S-methyl-PGE_1 ethyl ester (33) R; Et, is shown in FIG. 6.

Mass (SIMS) m/z: 411 $(M+H)^+$, 393 $((M+H)^+-18)$, 375, 347, 301, 149, 130.

EXAMPLE 9 (SEE CHART IV)

Synthesis of 13,14-Dihydro-6,15-diketo-16R, S-methyl-PGE_1 methyl ester (33), R=Me:

The title compound (33) was prepared from the methyl ester (27) following the same manner as the preparation of 13,14-dihydro-6,15-diketo-16R,S-methyl-PGE_1 ethyl ester (33).

The n. m. r. spctrum of the 13,14-dihydro-6,15-diketo-16R,S-methyl-PGE_1 methyl ester (33) is shown in FIG. 7.

Mass (SIMS) m/z: 397 $(M+H)^+$, 379 $((M+H)^+-18)$, 365, 347, 301, 143, 121, 111.

EXAMPLE 10 (SEE CHART V)

Preparation of 13,14-Dihydro-15-keto-3R,S,16R,S-dimethyl-PGE_2-methyl ester (36)

10 - 1 Preparation of 13,14-Dihydro-15,15-ethylene dioxy-3R,S,16R,S-dimethyl-11-(2-tetrahydropyranyl-)oxy-$PGE_{2\alpha}$ methyl ester (34):

Sodium hydride (60%, 0.4660 g), washed with dry ether, was suspended in dry DMSO (8 ml), and the suspension was stirred at 60° C. for 1 h. A DMSO solution of (3R,S-methyl-4-carboxybutyl)triphenylphosphonium bromide (2.66 g) was added to sodium methylsulfinyl carbonion to give deep red ylide. After addition, the reaction solution was stirred for 15 minutes. A DMSO solution (10 ml) of lactol (25) (0.8 g) was added dropwise, and the mixture was agitated overnight. The reaction solution was poured in ice-water and adjusted to pH 12 with 10% sodium hydroxide solution, and then extracted with ether. The aqueous layer was adjusted to pH 5-6 with 1-N hydrochrolic acid and then extracted with ether. The organic extract of the acidic aqueous solution was dried, and concentrated under reduced pressure. The crude product thus obtained was esterified with diazomethane and then was chromatographed to give 13,14-dihydro-3R,S, 16R,S-dimethyl-15,15-ethylenedioxy-11-(2-tetrahydropyranyl)oxy-PGE_2 methyl ester (34). Yield: 0.7483 g.

10 - 2 Preparation of 13,14-Dihydro-15-keto-3R,S, 16R,S-dimethyl-PGE_2 methyl ester (36):

According to the manner analogous to the Examples 2 to 9 with using the PGF_2 derivative (34), 13,14-dihydro- 15-keto-3R,S, 16R,S-dimethyl-PGE_2 methyl ester (36) was produced.

The n. m. r. spectrum of 13,14-dihydro-15-keto-3B,S,16R,S,S-dimethyl-PGE_2 methyl ester (36) is shown in FIG. 8.

Mass (SIMS) m/z: 395 $(M+H)^+$, 377 $((M+H)^+-18)$, 345, 121, 109, 95.

EXAMPLE 11 (SEE CHART VI)

Preparation of 13,14-Dihydro-6,15-diketo-16R,S-fluoro-PGE_1 ethyl ester (50)

11 - 1 Preparation of 1S-2-Oxa-3-oxo-6R-(4R, S-fluoro-3-oxo-1-trans-octenyl)-7R-(4-phenylbenzoyl-)oxy-cis-bicyclo (3, 3, 0) octane (37):

Sodium hydride (60%, 1.70 g) was suspended in THF, and a THF solution of dimethyl(3R,S-fluoro-2-oxoheptyl)phosphonate (4) (10.23 g) was added to the suspension, and agitated at room temperature for 20 min. To the mixture was added a THF solution of aldehyde (2) which was obtained after Collins-oxidation of the (−)-lactone (1) (15.00 g).

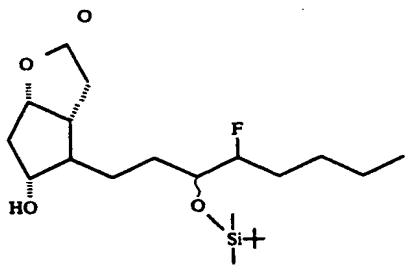
After 2 h agitation at room temperature, the reaction solution was neutralized with acetic acid (15 ml). Thereafter, a residue obtained after the usual work-up was purified by column-chromatography (ethyl acetate: hexane=1:2) to give a colorless oily enone (37) Yield: 10.45 g (53%).

11 - 2 Preparation of 1S-2-Oxa-3-oxo-6R-(4R, S-fluoro-3R,S-hydroxy-1-octyl)-7R-(4-phenylbenzoyl-)oxy-cis-bicyclo (3, 3, 0) octane (39):

The enone (37) (10.45 g) was hydrogenated with 5% palladium or carbon (1.0 g) and hydrogen in ethyl acetate (50 ml) to give ketone (38). Yield: 9.35 g (89%).

The ketone (38) (9.35 g) was reduced with sodium borohydride (1.15%) in absolute methanol (200 ml) to give a colorless oily substance (39). Yield: 6.50 g (69%).

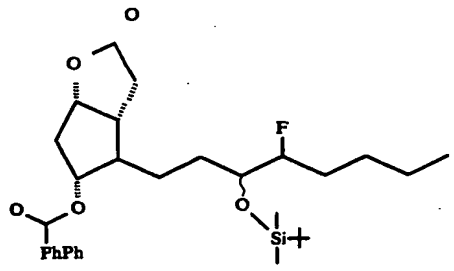
11 - 3 Preparation of 1S-2-Oxa-3-oxo-6R-(4R,S-fluoro-3R,S-t-butyldimethylsilyloxy-1-octyl)-7R-hydroxy-cis-bicyclo(3, 3, 0)octane (41):



(41)

The alcohol (39) (6.50 g) was converted with t-butyldimethylsilyl chloride (6.27 g) and imidazole (5.67 g) in

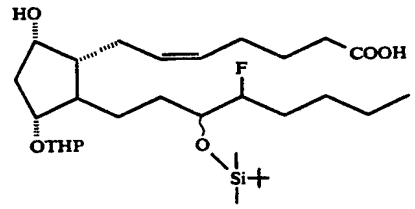
dry DMF (30 ml) to the corresponding t-butyldimethylsilyl ether (40). Yield: 8.80 g (100%).



(40)

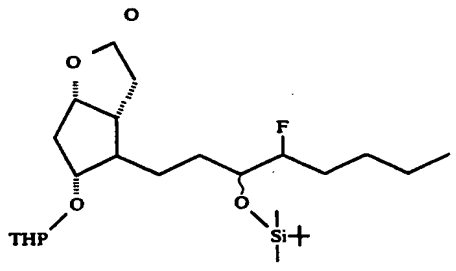
The t-butyldimethylsilyl ether (40) (8.80 g) was dissolved in methanol (80 ml), and anhydrous potassium carbonate (2.09 g) was added to the solution. The reaction was stirred for 4 h at room temperature. A colorless oily alcohol (41) was obtained after the usual work-up, and purification. Yield: 4.11 g (67%).

11 - 4 Preparation of 13,14-Dihydro-16R,S-fluoro-15R,S-t-butyldimethylsilyloxy-11-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ (44):



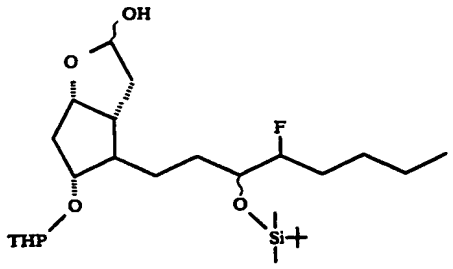
(44)

The alcohol (41) (4.11 g) was dissolved in dry dichloromethane (50 ml), and dihydropyran (4.10 ml) and p-toluenesulufonic acid (catalytic amount) were added to the solution. The reaction solution was stirred at room temperature for 10 min. The residue obtained after usual work-up was chromatographed (ethyl acetate: hexane=1:4~1:3) to give a colorless oily tetrahydropyranyl ether (42). Yield 5.08g (100%).



(42)

The tetrahydropyranyl ether (42) (5.08 g) was reduced with DIBAL-H (1.5M, 20 ml) in dry toluene (60 ml) at −78° C., and a colorless oily lactol (43) was obtained.



(43)

Ylide was prepared from (4-carboxybutyl) triphenylphosphonium bromide (18.51 g) according to the usual procedure, and to this ylide was added a DMSO solution of the previously prepared lactol (43). The reaction solution was stirred at room temparature for 2 h. The residue obtained after the usual work-up was dissolved in ether. After insoluble material was separated by filtration, the filtrate was concentrated under reduced pressure, and a crude carboxylic acid (44) was obtained. Yield: 8.0 g.

11 - 5 Preparation of 13,14-Dihydro-16R,S-fluoro-15R,S-hydroxy-11-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ ethyl ester (46):

The crude carboxylic acid (44) (8.0 g) was dissolved in dry acetonitrile (40 ml), and DBU (3.0 ml) and ethyl iodide (6.0 ml) were added, and agitated at 60° C. for 60 min. The residue obtained after usual work-up was chromatographed (with ethylacetate: hexane=1:4~1:2) to give a colorless oily ester (45). Yield: 1.84 g.

The ester (45) (1.84 g) was dissolved in dry THF (30 ml), and tetrabutylammonium fluoride (1.0-M, 45 ml) was added. The reaction solution was stirred at room temperature for 3.5 h. The reside obtained after the usual work-up was chromatographed (ethyl acetate: hexane=1:2~1:3) to give a colorless oily alcohol (46). Yield: 1.34 g (90%).

11 - 6 Preparation of 13,14-Dihydro-16R,S-fluoro-15R,S-hydroxy-6-keto-11-(2-tetrahydropyranyl)oxy-PGF_2 ethyl ester (48):

The alcohol (46) (0.6254 g) was dissolved in dry dichloromethane (30 ml) and dry THF (3 ml), and N-bromosuccinimide (0.229 g) were added. The reaction solution was stirred for 10 min. The residue obtained after the usual work-up was chromatographed (ethyl acetate: hexane=2:3) to give a colorless oily bromo-ether (47). Yield: 0.6837 g (94%).

The bromo-ether (47) (0.8243 g) was dissolved in dry toluene (20 ml) and DBU (2.20 ml). The mixture was stirred at 65° C. overnight. After addition of water to the reaction solution, the mixture was acidified with dilute hydrochloric acid under ice cooling, and was extracted with ethyl acetate. The residue obtained after the usual work-up was chromatographed (ethyl acetate: hexane=1:1~2:1) to give a colorless oily 6-keto substance (48). Yield: 0.482 g (66%).

11 - 7 Preparation of 13,14-Dihydro-6,15-diketo-16R,S-fluoro-PGE_1 ethyl ester (50):

The dialcoholic substance (48) (0.230 g) was oxidized in acetone (20 ml) at −10° C. to −8° C. with Jones reagent (2.67M, 1.5 ml).

The residue obtained after the usual work-up was chromatographed (with ethyl acetate: hexane=1:2) to

give a colorless oily keto substance (49). Yield: 0.100 g (44%)

The tetrahydropyranyl ether (49) (0.200 g) was dissolved in a mixed solvent (20 ml) of acetic acid: water: THF (4:2:1), and the solution was stirred at 47° C. for 3 hours.

The reaction solution was concentrated under reduced pressure, and the resulting residue %las chromatographed (ethyl acetate: hexane=1:1) to give 13,14-dihydro-6,15-diketo-16R,S-fluoro-PGE_1 ethyl ester (50). Yield: 0.153 g (92%).

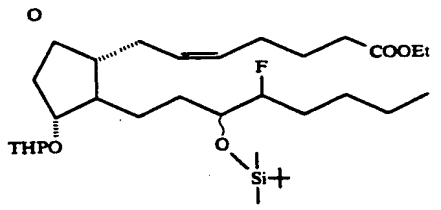
The n. m. r. spectrum of 13,14-dihydro-6,15-diketo-16R,S-fluoro-PGE_1 ethyl ester (50) is shown in FIG. 9.

Mass (SIMS) m/z: 415 $(M+H)^+$, 397 $((M+H)^+-18)$, 377, 351, 305, 157, 111.

EXAMPLE 12 (SEE CHART VII)

Preparation of 13,14-Dihydro-15-keto-16R,S-fluoro-11R-dehydroxy-11R-methyl-PGE_2 ethyl ester (54)

12 - 1 Preparation of 13,14-Dihydro-15R,S-t-butyldimethylsilyloxy-16R,S-fluoro-11-(2-tetrahydropyranyl) oxy-PGE_2 ethyl ester (51):



(51)

The alcohol (45) (0.506 g) was oxidized (2.67M) in acetone at −30° C. with Jones reagent. The crude product obtained after the usual work-up was chromatographed (ethyl acetate: hexane=2:9) to give a ketonic substance (51). Yield: 0.380 g (75%).

12 - 2 Preparation of 13,14-Dihydro-16R,S-fluoro-15R,S-hydroxy-PGA_2 ethyl ester (52):

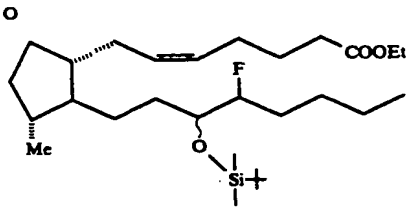
The tetrahydropyranyl ether (51) was dissolved in 23 ml of a mixed solvent of acetic acid and water (20:3), and the solution was stirred at 70° C. The reactant was concentrated under reduced pressure, and then was chromatographed (ethyl acetate: hexane=1:3∼1:1) to give a colorless oily enone (52). Yield: 0.078 g (32%).

12 - 3 Preparation of 13,14-Dihydro-15-keto-16R,S-fluoro-11R-dehydroxy-11R-methyl-PGE_2 ethyl ester (54):

Cuprous iodide (0.318 g) was suspended in anhydrous ether (30ml), and methyl lithium (15-M; 2.23 ml) was added dropwise to the suspension at −13° C. to give a clear solution, to which the enone (52) (0.080 g) in ether (20 ml) was added. The reaction solution was stirred for 45 min. Then, acetic acid (0.84 ml) was added. The mixture was poured into an aqueous ammonium chloride, and extracted with ether.

The extract was washed, dried, and then concentrated under reduced pressure. The resulting crude product was chromatographed (ethyl acetate: hexane=2:5) to give a colorless oily alcoholic substance (53). Yield: 0.075 g (90%).

The alcoholic substance (53) (0.136 g) was oxidized with Jones reagent (2.67M) in acetone (20 ml) at −10° C. to −8° C. A crude product obtained after the usual work-up was chromatographed (ethyl acetate: hexane=1:4) to give colorless oily 13,14-dihydro-15-keto-16R,S-fluoro-11R-dehydroxy-11R-methyl-PGE_2 ethyl ester (54). Yield: 0.122 g (90%).



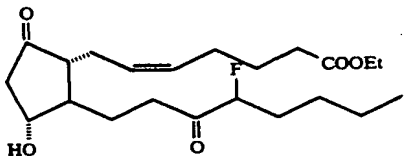
(53)

The n. m. r. spectrum of 13,14-dihydro-15-keto-16R,S-fluoro-11R-dehydroxy-11R-methyl-PGE_2 ethyl ester (54) is shown in FIG. 10.

Mass (SIMS) m/z: 397 $(M+H)^+$, 379 $((M+H)^+-18)$, 329, 301, 258, 237, 207, 167, 132.

EXAMPLE 13

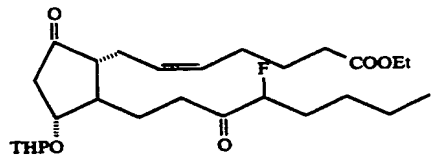
Preparation of 13,14-Ddihydro-15-keto-16R,S-fluoro-PGE_2 ethyl ester (56)



(56)

Diol (46) (chart VI) (0.501 g) was dissolved in acetone (35 mi) and was oxidized with Jones reagent at −35° C. (2.67-M; 1 ml).

The crude product obtained after the usual work-up was chromatographed to give a tetrahydropyranyl ether (55). Yield: 0.347 g (70%).



(55)

The tetrahydropyranyl ether (55) (0.347 g) was dissolved in 25 ml of a mixed solvent of acetic acid: THF: water (3:1:1), and the solution was stirred at 40° C. for 12 h.

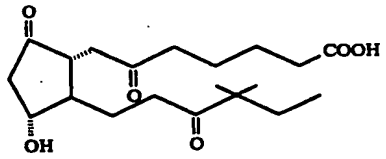
A crude product obtained after the usual work-up was chromatographed to give 13,14-dihydro-15-keto-16R,S-fluoro-PGE_2 ethyl ester (56). Yield: 0.204 g (71%).

The n. m. r. spectrum of 13,14-dihydro-15-keto-16R,S-fluoro-PGE_2 ethyl ester (56) is shown in FIG. 11.

Mass (D I) m/z: 398 $(M+H)^+$, 380 $(M^+- 18)$, 226, 109, 95, 81.

EXAMPLE 14

Preparation of 13,14-Dihydro-6,15-diketo-16,16-dimethyl-PGE_1 ethyl ester (57)



(57)

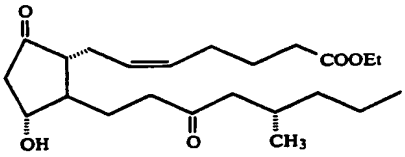
The title compound (57) was prepared following the procedure analogous to that in Example 2 to 13 with using (−)-Corey lactone (1) and dimethyl(3,3-dimethyl-2-oxoheptyl)phosphonate.

The n. m. r. spectrum of 13,14-dihydro-6,15-diketo-16,16-dimethyl-PGE_1 ethyl ester (57) is shown in FIG. 12.

Mass (D I) m/z: 398 $(M+H)^+$, 380 $(M^+ - 18)$, 226, 109, 95, 81.

EXAMPLE 15

Preparation of 13,14-Dihydro-15-keto-17S-methyl-PGE_2 ethyl ester (58)



(58)

The same procedure as in Examples 1 to 14 was followed using dimethyl (4S-methyl-2-oxoheptyl)phosphonate and (−)- Corey lactone (1), and thus 13,14-Dihydro-15-keto-17S-methyl-PGE_2 ethyl ester (58) was synthesized.

The n. m. r. spectrum of 13,14-dihydro-15-keto-17S-methyl-PGE_2 ethyl ester (58) is shown in FIG. 13.

Mass (D I) m/z: 394 (M^+), 376 $(M^+ - 18)$, 222, 109, 94.

EXAMPLE 16 (SEE CHART VIII)

Preparation of 13,14-Dihydro-15-keto-19-methyl-PGE_2ethyl ester (60), R=Et:

Same procedure as in Examples 2 to 15 was followed using the unsaturated ketone (59) obtained from dimethyl (6-methyl-2-oxoheptyl)phosphonate and (−)-Corey lactone (1), and thus 13, 14-dihydro-15-keto-19-methyl-PGE_2 ethyl ester (60) was synthesized.

The n. m. r. spectrum of 13,14-dihydro-15-keto-19-methyl-PGE_2 ethyl ester (60) is shown in FIG. 14.

Mass (D I) m/z: 394 (M^+) 376 $(M^+ - 18)$, 331, 222, 109, 95, 94.

EXAMPLE 17 (SEE CHART VIII)

Preparation of 13,14-dihydro-15-keto-19-methyl-PGE_2methyl ester (61), R=Me

Preparation was carried out using the unsaturated ketone (59) and the same way as in Examples 2 to 16.

The n. m. r. spectrum of 13,14-dihydro-15-keto-19-methyl-PGE_2 methyl ester (61) is shown in FIG. 15.

Mass (D I) m/z: 380 (M^+), 362 $(M^+ - 18)$, 331, 222, 109, 95, 94.

EXAMPLE 18 (SEE CHART VIII)

Preparation of 13,14-Dihydro-6,15-diketo-19-methyl-PGE_1 ethyl ester (62), R=Et

Preparation was carried out using the unsaturated ketone (59) and the same way as in Examples 2 to 17.

The n. m. r. spectrum of 13,14-dihydro-6,15-diketo-19-methyl-PGE_1 ethyl ester (62) is shown in FIG. 16.

Mass (SIMS) m/z: 411 $(M+M)^+$, 393 $((M+H)^+ - 18)$, 323, 292, 291, 217, 201, 109.

EXAMPLE 19 (SEE CHART VIII)

Preparation of 13,14-Dihydro-6,15-diketo-19-methyl-PGE_1 methyl ester (63), R=Me

Preparation was carried out using the unsaturated ketone (59) and the same way as in Examples 2 to 18.

The n. m. r. spectrum of 13,14-dihydro-6,15-diketo-19-methyl-PGE_1 methyl ester (63) is shown in FIG. 17.

Mass (D I) m/z: 369 (M^+), 378 $((M^+ - 18)$, 265, 235, 143, 111.

EXAMPLE 20

Preparation of 13,14-Dihydro-15-keto-16,16-dimethyl-20-methoxy-PGE_2 methyl ester (64)

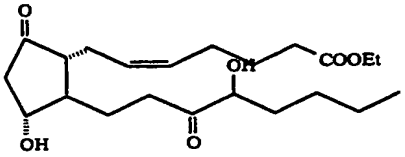
The same procedure as in Examples 2 to 19 was followed using dimethyl (3,3-dimethyl-7-methoxy-2-oxoheptyl)phosphonate and (−)-Corey lactone (1), and thus 13,14-dihydro-15-keto-16,16-dimethyl-20-methoxy-PGE_2 methyl ester (64) was prepared.

The n. m. r. spectrum of 13,14-dihydro-15-keto-16,16-dimethyl-20-methoxy-PGE_2 methyl ester (64) is shown in FIG. 18.

Mass (E I) m/z: 424 (M^+), 406 $((M^+ - 18)$, 375, 266, 375, 266, 245, 217, 129.

EXAMPLE 21

Preparation of 13,14-Dihydro-15-keto-16R,S-hydroxy-PGE_2 ethyl ester (65)



(65)

The same procedure as in Examples 2 to 20 was followed using (−)-Corey lactone (1) and dimethyl(3-(2-tetrahydropyranyl)oxy-2-oxoheptyl)phosphonate, and thus 13,14-dihydro-15 keto-16R,S-hydroxy PGE_2 ethyl ester (65) was synthesized.

The n. m. r. spectrum of 13,14-dihydro-15 keto-16R,S-hydroxy-PGE_2 ethyl ester (65) is shown in FIG. 19.

Mass (D I) m/z: 396 (M^+), 378 $((M^+ - 18)$, 333, 309, 96, 81.

EXAMPLE 22 (SEE CHART IX)

Preparation of 13,14-Dihydro-15-keto-PGE_1 ethyl ester(66), R: Et

22 - 1) Preparation of 13,14-Dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyloxy)-$PGF_{1\alpha}$ ethyl ester (64), R: Et

13,14-dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ ethyl ester (10), R=Et, (3.56 g) was hydrogenated with platinum oxide and hydrogen in ethanol (150 ml). After the usual work-up, there was obtained 3.50 g of 13,14-dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ ethyl ester (64).

22 - 2) Preparation of 13,14-Dihydro-15,15-ethylenedioxy-11-(2-tetrapyranyl)oxy-PGE_1 ethyl ester (65):

13,14-dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl)oxy-$PGF_{1\alpha}$ ethyl ester (64) (3.25 g) was oxidized with Jones reagent (2.67- M; 3.2 ml) in acetone (100 ml) at −300+ C. The crude product obtained after the usual work-up was chromatographed (hexane: ethyl acetate=5:2) to give 13,14-dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl) oxy-PGE_1 ethyl ester (65). Yield 2.72 g.

22 - 3) Preparation of 13,14-Dihydro-15-keto-PGE_1 ethyl ester (66):

13,14-Dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl)oxy-PGE_1 ethyl ester (65) (2.72 g) was dissolved in a mixed solvent (90 ml) of acetic acid: water: THF (4:2:1), and the solution was agitated for 3 h at 40°−45° C. The solvent was distilled off under reduced pressure, and the resulting crude product was chromatographed twice (hexane: ethyl acetate=1:1, and ethyl acetate: benzene=1:1) to give 13,14-dihydro-15-keto-PGE_1 ethyl ester (66).

The n. m. r. spectrum of 13,14-Dihydro-15-keto-PGE_1ethyl ester (66) is shown in FIG. 20.

EXAMPLE 23 (SEE CHART IX)

Preparation of 13, 14-Dihydro-15-keto-PGE_1 methyl ester (66), R: Me

The same procedure as in Example 22 was followed using 13,14-dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ a methyl ester (10), the compound obtained from the carboxylic acid (9) with diazomethane, and thus 13,14-dihydro-15-keto-PGE_1 methyl ester (66) was synthesized.

The n. m. r. spectrum of 13,14-dihydro-15-keto-PGE_1 ethyl ester (66) is shown in FIG. 21.

EXAMPLE 24 (SEE CHART X)

Preparation of 13,14-Dihydro-15-keto-PGE_2 methyl ester (68), R: Et

24 - 1) Preparation of 13,14-Dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl)-oxy-PGE_2 ethyl ester (67):

The ethyl ester (10) (3.4 g) was oxidized with Jones reagent acetone (150 ml) at −40° C., and ketone (67) was obtained. Yield: 2.6 g.

24 - 2) Preparation of 13,14-Dihydro-15-keto-PGE_2 ethyl ester (68):

Ketone (67) (2.6 g) was dissolved in a mixed solvent (20 ml) of acetic acid: water: THF (4:2:1), and the solution was kept at 40°-50° C. for 3 h. Following the usual procedures, there was obtained 1.4 g of 13,14-dihydro-15-keto-PGE_2 ethyl ester (68).

The n. m. r. spectrum of 13,14-dihydro-15-keto-PGE_2 ethyl ester (68) is shown in FIG. 22.

EXAMPLE 25 (SEE CHART X)

Preparation of 13,14-Dihydro-15-keto-PGE_2 methyl ester (68), R=Me

The procedure of Example 24 was repeated, except that the carboxylic acid (9) was converted to the corresponding methyl ester (10) with diazomethane, and thus 13,14-dihydro-15-keto-PGE_2 methyl ester (68), R=Me, was obtained.

The n. m. r. spectrum of 13,14-dihydro-15-keto-PGE_2 methyl ester (68) is shown in FIG. 23.

EXAMPLE 26 (SEE CHART X)

Preparation of 13,14-Dihydro-15-keto-PGE_2 n-propyl ester (68), R=n-Pro

The same procedure as in Examples 24 and 25 was followed, except that the carboxylic acid 9 was converted to the corresponding n-propyl ester (10) with DBU and n-propyl iodide in acetonitrile, and thus 13,14-dihydro-15-keto-PGE_2 n-propyl ester (68) was obtained.

The n. m. r. spectrum of 13,14-dihydro-15-keto-PGE_2 n-propyl ester (68) is shown in FIG. 24.

EXAMPLE 27 (SEE CHART X)

Preparation of 13,14-Dihydro-15-keto-PGE_2 isopropyl ester (68), R=iso-Pro

The same procedure as in Examples 24, 25, and 26 was followed, except that the carboxylic acid (9) was converted to the corresponding isopropyl ester (10) with DBU and isopropyl iodide in acetonitrile, and thus 13,14-dihydro-15-keto-PGE_2 isopropyl ester (68) was obtained.

The n. m. r. spectrum of the 13,14-dihydro-15-keto-PGE_2 isopropyl ester (68) is shown in FIG. 25.

EXAMPLE 28 (See Chart X)

Preparation of 13,14-Dihydro-15-keto-PGE_2-n-butyl ester (68), R=n-Bu

The same procedure as in Examples 24, 25, 26, and 27 was followed, except that the carboxylic acid (9) was converted to the corresponding n-butyl-ester (10) with DBU and n-butyl iodide in acetonitrile, and thus 13,14-dihydro-15-keto-PGE_2n-butyl ester (68) was obtained.

The n. m. r. spectrum of 13,14-dihydro-15-keto-PGE_2 n-butyl ester (68) is shown in FIG. 26.

EXAMPLE 29 (SEE CHART X)

Preparation of 13, 14-Dihydro-15-keto-PGE_2 cyclopentyl ester (68), R=cyclopentyl

The same procedure as in Examples 24, 25, 26, 27, and 28 was followed, except that the carboxylic acid (9) was converted to the corresponding cyclopentyl-ester (10) with DBU and cyclopentyl iodide in acetonitrile, and thus 13,14-dihydro-15-keto-PGE_2 cyclopentyl ester (68) was obtained.

The n. m. r. spectrum of 13,14-dihydro-15-keto-PGE_2 cyclopentyl ester (68) is shown in FIG. 27.

EXAMPLE 30 (SEE CHART X)

Preparation of 13,14-Dihydro-15-keto-PGE_2 benzyl ester (68), R=Benzyl

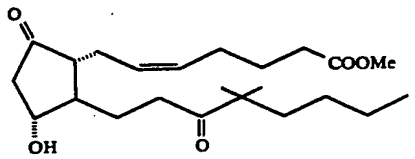
The same procedure as in Examples 24, 25, 26, 27, 28, and 29 was followed, except that the carboxylic acid (9) was converted to the corresponding benzyl ester (10) with DBU and benzyl bromide in acetonitrile, and thus 13,14-dihydro-15-keto-PGE_2-benzil ester (68) was obtained.

The n. m. r. spectrum of 13,14-Dihydro-15-keto-PGE_2 benzyl ester (68) is shown in FIG. 28.

EXAMPLE 31

Preparation of 13,14-Dihydro-15-keto-16,16-dimethyl-PGE_2 methyl ester (69), R=Me

(69)



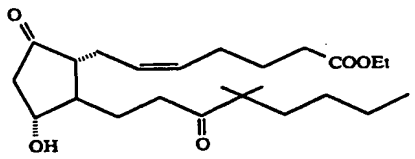
The same procedure as in Examples 24 to 30 was followed using(−)-Corey lactone (1) and a dimethyl (3,3-dimethyl-2-oxoheptyl)phosphonate obtained in the ordinary method, to produce 13,14-dihydro-15-keto-16,16-dimethyl-PGE_2 methyl ester (69).

The n. m. r. spectrum of 13,14-dihydro-15-keto-16,16-dimethyl-PGE_2 methyl ester (69) is shown in FIG. 29.

EXAMPLE 32

Preparation of 13,14-Dihydro-15-keto-16,16-dimethyl-PGE_2 ethyl ester (70), R=Et

(70)



The same procedure as in Examples 24 to 31 was followed using(−)-Corey lactone (1) and dimethyl (3,3-dimethyl-2-oxoheptyl)phosphonate to produce 13,14-dihydro-15-keto-16,16-dimethyl-PGE_2 ethyl ester (70).

The n. m. r. spectrum of 13,14-Dihydro-15-keto-16,16-dimethyl-PGE_2ethyl ester (70) is shown in FIG. 30.

EXAMPLE 33 (SEE CHARTS X AND XI)

Preparation of 13,14-Dihydro-15-keto-3 R,S-methyl-PGE_2 ethyl ester (74)

13,14-Dihydro-15-keto-3R,S-methyl-PGE_2 ethyl ester (74) was obtained by following the same procedure as in Examples 24 to 30 except that ylide prepared from (3-methyl- 4-carboxybutyl)triphenylphosphonium bromide, and that the lactol (8), were used to produce 13,14-dihydro-15,15-ethylenedioxy-3-methyl-11-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ (71).

The n. m. r. spectrum of 13,14-dihydro-15-keto-3 R,S-methyl-PGE_2 ethyl ester (74) is shown in FIG. 31.

EXAMPLE 34 (SEE CHARTS X AND XII)

Preparation of 13,14-Dihydro-15-keto-20-methoxy-PGE_2 methyl ester (79)

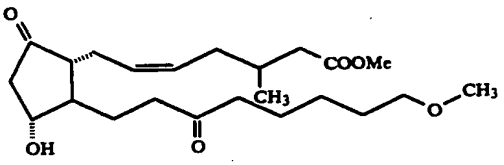
The same procedure as in Examples 24 to 30 was followed using(−)-Corey lactone (1) and dimethyl (7-methoxy-2-oxoheptyl)phosphonate produced in the ordinary method, and thus 13,14-dihydro-15-keto-20-methoxy-PGE_2 methyl ester (79) was obtained.

The n. m. r. spectrum of 13,14-dihydro-15-keto-20-methoxy-PGE_2 methyl ester (79) is shown in FIG. 32.

EXAMPLE 35 (SEE CHART XII)

Preparation of 13,14-Dihydro-15-keto-3R,S-methyl-20-methoxy-PGE_2 methyl ester (80)

(80)



The same procedure as in examples 24 to 30, 33 and 34 was followed using lactol (75) and (3-methyl-4-carboxybutyl) triphenylphosphonium bromide produced in the usual manner, and thus 13,14-Dihydro-15-keto-3R,S-methyl-20-methoxy-PGE_2 methyl ester (80) was obtained.

The n. m. r. spectrum of 13,14-Dihydro-15-keto-3R,S-methyl-20-methoxy-PGE_2 methyl ester (80) is shown in FIG. 33.

EXAMPLE 36 (SEE CHART XIII)

Preparation of 13,14-Dihydro-15-keto-Δ^2-PGE_2 methyl ester (85), R=H

36 - 1) 11-(t-Butyldimethylsilyl)oxy-13,14-Dihydro-15,15-ethylenedioxy-2-phenylselecyl-$PGF_{2\alpha}$ methyl ester (82):

LDA was prepared from diisopropyl- amine (0.13 ml) in dry THF (3 ml), and n-butyl lithium (1.6 - M; 0.58 ml), at −78° C. To LDA was added 0.1850 g of (81) in THF, and stirred for 1.5 h. A dry THF solution (2 ml) of diphenyl diselenide (0.18 g) was added, and the reaction solution was stirred at −78° C. for 30 min, then at room temperature for 1 h. Following usual procedure, there was obtained 0.1366 g of 2-phenylselenyl-$PGF_{2\alpha}$ methyl ester (82).

36 - 2) Preparation of 11-(t-Butyldimethylsilyl) oxy-13,14-dihydro-15,15-ethylenedioxy-Δ^2-$PGF_{2\alpha}$ methyl ester (83):

The 2-Phenylselenyl-$PGF_{2\alpha}$ methyl ester (82) (0.1366 g) was dissolved in a mixed solvent (4 ml) of ethyl acetate- THF (1:1), and sodium hydrogen carbonate (0.1 g) and 30% hydrogen pereoxide (0.3 ml) were added. The reaction solution was stirred at room temperature for 15 min. Following the usual procedures, there was obtained 0.0850 g of 11-(t-butyldimethylsilyl)oxy-13,14-dihydro-15,15-ethylene dioxy-Δ^2-$PGF_{2\alpha}$ methyl ester (83). Yield: 0.0850 g.

36 - 3) Preparation of 11-(t-butyldimethylsilyl) oxy-13,14-Dihydro-15,15-ethylenedioxy-Δ^2-PGE_2 methyl ester (84).

The Δ^2-$PGF_{2\alpha}$ methyl ester (83) (0.0717 g) was oxidized with PCC on aluminum oxide (1 g) in benzene (2 ml). Following the usual procedures, there was obtained 0.0554 g of Δ^2-PGE_2 methyl ester (84). Yield: 0.0554 g.

36 - 4) Preparation of 13,14-Dihydro-15-keto-Δ^2-PGE_2 methyl ester (85):

Δ^2-PGE_2 methyl ester (84) (0.0554 g) was dissolved in acetonitrile (2 ml), and a mixture (1.5 ml) of 46%-aqueous hydrogen fluoride and acetonitrile (1:2) was added. The reaction solution was stirred at room temperature for 50 min. Following the usual procedures, there was obtained 13,14-Dihydro-15-keto-Δ^2-PGE_2 methyl ester (85). Yield: 0.0312 g.

The n. m. r. spectrum of 13,14-dihydro-15 keto-Δ^2-PGE_2 methyl ester (85) is shown in FIG. 34.

EXAMPLE 37 (SEE CHART XIII)

Preparation of 13,14-Dihydro-15-keto-20-methoxy-Δ^2-PGE_2 methyl ester (85), R=-OMe

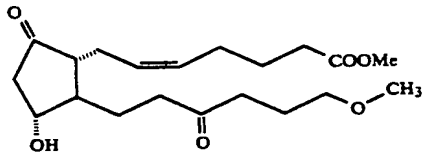
The same procedure as in Examples 24 to 30, 34 and 36 was followed with using(−)-Corey lactone (1) and dimethyl-(7-methoxy-2-oxoheptyl)phosphonate, and thus 13, 14-dihydro-15-keto-20-methoxy-Δ^2-PGE_2 methyl ester (85), R=- OMe, was obtained.

The n. m. r. spectrum of 13,14-Dihydro-15-keto-20-methoxy-Δ^2-PGE_2 methyl ester (85) is shown in FIG. 35.

EXAMPLE 38

Preparation of 13,14-Dihydro-15-keto-18-methoxy-19, 20-bisnor-PGE_2 methyl ester (86)

(86)



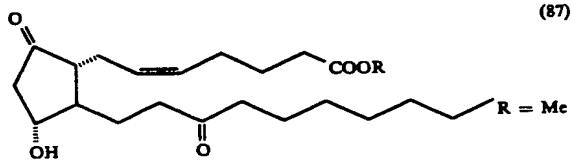
The same procedure as in Examples 24 to 30, and 34 was followed with using(−)-Corey lactone (1) and dimethyl (5-methoxy-2-oxopentyl)phosphonate, and thus 13,14-dihydro-15-keto-18-methoxy-19,20-bisnor-PGE_2 methyl ester (86) was obtained.

The n. m. r. spectrum of 13,14-Dihydro-15-keto-18-methoxy-19,20-bisnor-PGE_2 methyl ester (86) is shown in FIG. 36.

EXAMPLE 39

Preparation of 13,14-Dihydro-15-keto-20-ethyl-PGE_2 methyl ester (87), R=Me

(87)



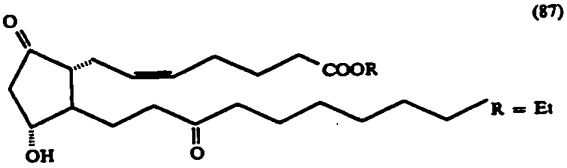
The same procedure as in Examples 24 to 30 was followed with using(−)-Corey lactone (1) and dimethyl(2-oxononyl)phosphonate, and thus 13,14-dihydro-15-keto-20-ethyl-PGE_2 methyl ester (87) was obtained.

The n. m. r. spectrum of 13,14-Dihydro-15-keto-20-ethyl-PGE_2-methyl ester (87) is shown in FIG. 37.

EXAMPLE 40

Preparation of 13,14-Dihydro-15-keto-20-ethyl-PGE_2 ethyl ester (87), R=Et

(87)



The same procedure as in Examples 24 to 28 was followed with using(−)-Corey lactone (1) and dimethyl(2-oxononyl)phosphonate produced with the known method, and thus 13,14-Dihydro-15-keto-20-ethyl-PGE_2 ethyl ester (87) was obtained.

The n. m. r. spectrum of 13,14-Dihydro-15-keto-20-ethyl-PGE_2-ethyl ester (87), R=Et, is shown in FIG. 38.

Mass(DI) m/z: 408, 390, 345.

EXAMPLE 41 (SEE THE STRUCTURAL FORMULA (87) SHOWN IN EXAMPLE 39)

Preparation of 13,14-Dihydro-15-keto-20-ethyl-PGE_1 methyl ester (88)

13,14-Dihydro-15-keto-20-ethyl-PGE_2methyl ester (87), R=Me, obtained in the same way as in Example 39 was hydrogenated with plutinum oxide and hydrogen in ethanol, and thus 13,14-Dihydro-15-keto-20-ethyl-PGE_1 methyl ester (88) was prepared.

The n. m. r. spectrum of 13,14-Dihydro-15-keto-20-ethyl-PGE_1 methyl ester (88), R=Me, is shown in FIG. 39.

EXAMPLE 42

Preparation of 13,14-Dihydro-15-keto-20-n-propyl-PGE_2 methyl ester (89)

The same procedure as in Examples 24 to 30 and 39 was followed using(−)-Corey lactone (1) and dimethyl(2-oxodecyl)phosphonate produced according to the known method, and thus 13,14-Dihydro-15-keto-20-n-propyl-PGE_2methyl ester (89) was synthesized.

The n. m. r. spectrum of 13,14-Dihydro-15-keto-20-n-propyl-PGE_2methyl ester (89) is shown in the FIG. 40.

Mass (SIMS): 409, 391, 369.

EXAMPLE 43 (SEE CHART XIV)

Preparation of 13,14-Dihydro-15-keto-20 -ethyl-11R-dehydroxy-11R-methyl-PGE_2methyl ester (98)

43 - 1) Tosylation of 1S-2Oxa-3-oxo-6R-(3,3-ethylenedioxy-1-decyl)-7R-hydroxy-cis-bicyclo (3,3,0)octane (90): Preparation of tosylate (91):

Alcohol (90) (1.723 g) was treated with p-toluenesulfonyl chloride (2.893 g) in pyridine (5 ml) to give the tosylate(91). Yield: 1.812 g (74%).

43 - 2) Preparation of 1S-2-Oxa-3-oxo-6S-(3, 3-ethylenedioxy-1-decyl)-cis-bicyclo(3,3,0)oct-7-ene (92):

DBU (5.6 ml) was added to a toluene solution (1.9 ml) of the tosylate (91) (1.812 g), and the reaction solution

was kept at 60° C. for 7 h. A crude product obtained after the usual work-up was chromatographed (hexane-ethyl acetate=3:1) to give the olefin (92).

Yield: 0.7594 g (63%).

43 - 3) DIBAL-H reduction of 1S-2-Oxa-3-oxo-6S-(3,3ethylenedioxy-1-decyl)-cis-bicyclo(3,3,0)-oct-7-ene (92): Preparation of lactol (93):

The olefin (92) (0.7594 g) was treated with DIBAL-H (1.5 - M; 6.2 ml) to produce the lactol (93).

43 - 4) Preparation of methyl 15,15-Ethylenedioxy-20-ethyl-9S-hydroxy-cis-Δ^5-Δ^{10}- prostanoate (95):

The lactol (93) was added to a ylide generated from (4-carboxybutyl)triphenylphosphonium bromide and sodium methylsulfinyl carbanion, in DMSO, whereby prostanoic acid (94) was obtained. The acid (94) was esterified with diazomethane, and thus methyl 20-ethyl-prostanoate (95) was obtained.

Yield: 0.6600 g (67%).

43 - 5) Preparation of 15,15-Ethylenedioxy-20-ethyl-13,14-dihydro-PGA_2 methyl ester (96):

The methyl 20-ethyl-prostanoate (95) (0.6600g) was oxidized with Jones reagent in acetone (400 ml) at −20° C. The crude material obtained after the usual work-up was chromatographed (hexane-ethyl acetate=3:1) to give 15,15-ethylenedioxy-20-ethyl-13,14-dihydro-PGA_2 methyl ester (96).

Yield: 0.6182 g (99%).

43 - 6) Preparation of 15,15-Ethylenedioxy-20-ethyl-13,14-dihydro-11R-dehydroxy-11R-methyl PGE_2 methyl ester (97):

The enone (96) (0.6100 g) was treated with lithium dimethylcuprate obtained from copper (I) iodide (0.8380 g) and methyl lithium (1.5 - M; 5.8 ml), in ether (15 ml), and there was obtained 15,15-ethylenedioxy-20-ethyl-13,14-dehydroxy-11R-dihydroxy-11R-methyl PGE_2 methyl ester (97).

Yield: 0.5720 g (94%).

43 - 7) Preparation of 13,14-Dihydro-15-keto-20-ethyl-11R-dehydroxy-11R-methyl-PGE_2 methyl ester (98):

15,15-Ethylenedioxy-20-ethyl-13,14-dihydro-11R-dehydroxy-11R-methyl-PGE_2 methyl ester (97) (0.2300 g) was dissolved in 25 ml of a mixed solvent of acetic acid: water: THF (3:1:1), and the solution was kept at 50° C. for 2 h. A crude product obtained after the usual work-up was chromatographed to give 13,14-dihydro-15-keto-20-ethyl-11R-dehydroxy-11R-methyl-PGE_2 methyl ester (98).

Yield: 0.200 g.

The n. m. r. spectrum of 13,14-dihydro-15-keto-20-ethyl-11R-dehydroxy-11R-methyl-PGE_2 methyl ester (98) is shown in FIG. 41.

Mass (DI) m/z: 392, 374, 361, 343.

EXAMPLE 44

Preparation of 13,14-Dihydro-15-keto-11R-dehydroxy-11R-methyl-PGE_2 ethyl ester (99)

The same procedure as in Example 43 was followed with using (−)-Corey lactone (1), dimethyl(2-oxoheptyl)phosphonate, and (4-carboxybutyl)triphenylphosphonium bromide, and 13,14-dihydro- 15-keto-11R-dehydroxy-11R-methyl-PGE_2 ethyl ester (99) was produced.

The n. m. r. spectrum of 13,14-dihydro-15-keto-11R-dehydroxy-11R-methyl-PGE_2 ethyl ester (99) is shown in FIG. 42.

Mass (SIMS) m/z: 387, 360, 333, 315.

EXAMPLE 45 (SEE CHART XV)

Preparation of 13,14-Dihydro-15-keto-20-isopropylidene-PGE_2 methyl ester (103)

1S-2-Oxa-3-oxo-6R-(8-isopropylidene-3-keto-1-trans-octenyl)-7R-(4-phenylbenzoyl)oxy-cis-bicyclo(3, 3, 0)-octane (100), a compound produced from(−)-Corey lactone (1) and dimethyl (2-oxo-7-isopropylideneheptyl)phosphonate, was converted to the corresponding silylenolether (101) with dimethylphenyl silane (0.9 ml) and Wilkinson catalyst (50 mg) in THF (40 ml). The silylenolether (101) was ketalized in benzene in the usual manner, and thus there was obtained 1S-2-oxa-3-oxo-6R-(8-isopropylidene-3,3-ethylenedioxy-1-octyl)-7R-(4-phenylbenzoyl)oxy-cis-bicyclo(3, 3, 0)octane (102).

Yield: 2.32 g (82%).

Subsequently, the same procedure as in Examples 24 to 30, 40, 41, and 42 was followed to produce 13,14-dihydro-15-keto-20-isopropylidene-PGE_2 methyl ester (103).

The n. m. r. spectrum of 13,14-dihydro-15-keto-20-isopropylidene-PGE_2 methyl ester (103) is shown in FIG. 43.

EXAMPLE 46 (SEE CHART XVI)

Preparation of 13,14-Dihydro-6,15-diketo-PGE_1 n-butyl ester (107), R=n - Bu

46 - 1) Preparation of the bromo-ether (104):

Bromo-ether formation from 15,15-ethylenedioxy-13,14-dihidro-11-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ n-butyl ester (10):

The butyl ester (10) (1.165 g) was dissolved in a THF-dichloromethane mixture (3 ml+30 ml), and the solution was ice-cooled. After addition of N-bromosuccinimide (0.405 g), the solution was stirred for 1 h. The reaction solution was poured in aqueous dilute sodium sulfite, and extracted with dichloromethane. The extract was dried, then concentrated under reduced pressure. The resulting crude product was chromatographed and thus bromo-ether (104) was obtained.

46 - 2) Preparation of 15,15-Ethylenedioxy-13,14-dihydro-6-keto-11-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ n-butyl ester (105):

Bromo-ether (104) (1.057 g) was dissolved in dry toluene (6 ml) and DBU (2.6 ml), and then agitated at 55° C. for 18 h. After being diluted with ethyl acetate, the mixture was adjusted to pH 3. Then, the organic layer of the solution was processed in the usual way.

Yield: 0.7132 g (75%).

46 - 3) Preparation of 15,15-Ethylenedioxy-13,14-dihydro-6-keto-11-(2-tetrahydropyranyl)oxy-PGE_2 n-butyl ester (106):

In acetone (40 ml), 6-keto-$PGF_{2\alpha}$ (105) (0.7132 g) was oxidized at −40° C. with Jones reagent, whereby 13,14-dihydro-15,15-ethylenedioxy-6-keto-11-(2-tetrahydropyranyl)oxy-PGE_2n-butyl ester (106) (0.4404 g) was obtained.

Yield: 0.4404 g (62%).

46 - 4) Preparation of 13,14-Dihydro-6,15-diketo-PGE_2n-butyl ester (107):

13, 14-Dihydro-15,15-ethylenedioxy-6-keto-11-(2-tetrahydropyranyloxy)-PGE_2 n-butyl ester (106) (0.4404 g) was kept at 55° C. in a mixed solvent of acetic acid: THF: water (3:1:1) for 3.5 h, whereby there was ob-

tained 13,14-dihydro-6,15-diketo-PGE_2 n-butyl ester (107).

Yield: 0.200 g (59%).

The n. m. r. spectrum of 13,14-dihydro-6,15-diketo-PGE_2 n-butyl ester (107) is shown in the FIG. 44.

EXAMPLE 47

Preparation of 13,14-Dihydro-6,15-diketo-20-methyl-PGE_2 ethyl ester (108):

The procedure of Example 46 was repeated with using(−)-Corey lactone (1) and dimethyl(2-oxooctyl)-phosphonate, and thus 13,14-dihydro-6,15-diketo-20-methyl-PGE_2 ethyl ester (108) was obtained.

The n. m. r. spectrum of 13,14-dihydro-6,15-diketo-20-methyl-PGE_2 ethyl ester (108) is shown in FIG. 45.

EXAMPLE 48 (SEE CHART XVII)

Preparation of 13,14-Dihydro-6,15-diketo-11R-dehydroxy-11 R-methyl PGE_1 ethyl ester (115), R=Et

48 - 1) Preparation of 15,15-Ethylenedioxy-13,14-dihydro-11R-dehydroxy-11R-methyl-$PGF_{2\alpha}$ ethyl ester (110):

15,15-Ethylenedioxy-13,14-dihydro-11R-dehydroxy-11R-methyl PGE_2 ethyl ester (109) (1.775 g), the compound obtained in the same way as in Example 43, was dissolved in a THF-methanol mixed solvent, and 0.1600 g of $NaBH_4$ was added. The solution was kept at −18° C. overnight. A crude product obtained after the usual work-up was chromatographed (hexane-ethyl acetate=3.5:1) to give.

9α-hydroxy substance (110): 0.9464 g;
9β-hydroxy substance (111): 0.5867 g.

The 9β-hydroxy substance (111) was oxidized with Jones reagent whereby 15,15-ethylenedioxy-13,14-dihydro-11R-dehydroxy-11R-methyl PGE_2 ethyl ester (109) was recovered, which was again reduced with $NaBH_4$. These reaction were repeated to amount to 1.446 g of 13,14-dihydro-15,15-ethylenedioxy-11R-dehydroxy-11 R-methyl-$PGF_{2\alpha}$ ethyl ester (110).

48 - 2) Preparation of Bromo-ether (112):

13,14-dihydro-15,15-ethylenedioxy-11R-dehydroxy-11R-methyl-$PGF_{2\alpha}$ ethyl ester (110) (1.446 g) was dissolved in a mixed solvent of THF (12 ml) and dichloromethane (3.5 ml), and NBS (0.6453 g) was added at −18° C. Following the usual procedure, there was obtained 1.932 g of bromo-ether (112).

48 - 3) Preparation of 15,15-Ethylenedioxy-13,14-dihydro-11R-dehydroxy-6-keto-11R-methyl-$PGF_{2\alpha}$ ethyl ester (113):

The bromo-ether (112) (1.932 g) was dissolved in DBU (6 ml) and toluene (3 ml), and the solution was kept at 75° C. A crude product obtained after the usual work-up was chromatographed (hexane-ethyl acetate=3:1) to give the title compound (113).

Yield: 1.230 g.

48 - 4) Preparation of 15,15-Ethylenedioxy-13,14-dihydro-11R-dehydroxy-6-keto-11R-methyl-PGE_1ethyl ester (114):

6-Keto-11R-methyl-$PGF_{2\alpha}$ ethyl ester (113) (1.230 g) was oxidized with Jones reagent in acetone, whereby 15,15-ethylenedioxy-13,14-dihydro-11R-dehydroxy-6-keto-11R-methyl-PGE_1 ethyl ester (114) was obtained.

Yield: 0.7614 g (62%) .

48 - 5) Preparation of 13,14-Dihydro-6,15-diketo-11R-dehydroxy-11R-methyl-PGE_1 ethyl ester (115):

15,15-Ethylenedioxy-13,14-dihydro-11R-11R-dehydroxy-11R-methyl-PGE_1 ethyl ester (114) (0.7614 g) was dissolved in a mixed solvent of acetic acid: THF: water (3:1:1), and the solution was kept at 50° C. for 5. Following the usual procedure, there was obtained 0.6290 g of 13,14-dihydro-6,15-diketo-11R-dehydroxy-11R-methyl-PGE_1ethyl ester (115), R=Et.

The n. m. r. spectrum of 13,14-dihydro-6,15-diketo-11R-dehydroxy-11R-methyl-PGE_1 ethyl ester (115) is shown in FIG. 46.

Mass (SIMS): 395 $(M+1)^+$, 377, 349.

EXAMPLE 49 (SEE CHART XVII)

Preparation of 13,14-Dihydro-6,15-diketo-11R-dehydroxy-11R-methyl-PGE_1 methyl ester (115), R=Me

The same procedure as in Example 48 was followed except that diazomethane was used for methyl-esterification, and thus there was obtained 13,14-dihydro-6,15-diketo-11R-dehydroxy-11R-methyl-PGE_1methyl ester (115), R=Me.

The n. m. r. spectrum of 13,14-dihydro-6,15-diketo-11R-dehydroxy-11R-methyl-PGE_1 methyl ester (115), R=Me, is shown in FIG. 47.

Mass (DI): 380, 362, 349, 331.

EXAMPLE 50 (SEE CHART XVIII)

Preparation of 13,14-Dihydro-15-keto-16R,S-fluoro-PGE_2methyl ester (125), R=Me

50 - 1) Preparation of 1S-2-oxa-3-oxo-6R-(4-fluoro-3-keto-1-octyl-7R-hydroxy-cis-bicyclo(3, 3, 0)octane (118):

A saturated ketone (117) (5.20 g) obtained after catalytic hydrogenation of the unsaturated ketone (116) produced from(−)-Corey lactone (1) and dimethyl(3-fluoro-2-oxoheptyl)phosphonate was dissolved in a mixed solvent (18 ml) of THF and methanol (3:1), and potassium carbonate (1.54 g) was added. The solution was stirred for 3 h.

The crude product obtained after the usual work-up was chromatographed (hexane: ethyl acetate=1:1) to yield an alcohol (118).

Yield: 1.81 g (57%).

50 - 2) Preparation of 1S-2-Oxa-3-oxo-6R-(4R,S-fluoro-3-oxo-1-octyl)-7R-(2-tetrahydropyranyl)oxy-cis-bicycle-(3, 3, 0) octane (119):

The alcohol (118) (1.81 g) was converted to the corresponding tetrahydropyranyl ether (119) with dihydrapyran and p-toluenesulfonic acid in dichloromethane.

Yield: 2.33 g.

50 - 3) Preparation of 1S-2-Oxa-3-oxo-6R-(4R,S-fluoro-3R,S-hydroxy-1-octyl)-7R-(2-tetrahydropyranyl) oxy-cis-bicyclo-(3, 3, 0)octane (120):

The tetrahydropyranyl ether (119) (2.33 g) was reduced with $NaBH_4$ in methanol. Alcoholic-lactone (120) was thus obtained.

50 - 4) Preparation of Lactol (121):

The alcoholic-lactone (120) (0.84 g) was reduced with DIBAL-H (1.5 - M, 6 ml) in toluene (20 ml) to the corresponding lactol (121).

50 - 5) Preparation of 16R,S-fluoro-13,14-dihydro-15R,S-hydroxy-11R-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ methyl ester (123), R=Me:

Ylide produced from (4-carboxybutyl)triphenyl~-phosphonium bromide (3.50 g) in the ordinary method was let to react with the previously synthesized lactol (121) in DMSO. A carboxylic acid (122) obtained according to the ordinary procedure was treated with diazomethane. Methyl ester (123) was thus obtained.

Yield: 0.470 g (44%).

50 - 6) Preparation of 13,14-Dihydro-15-keto-16R,S-fluoro-PGE$_2$methyl ester (125), R=Me:

The methyl ester (123) (0.470) was oxidized with Jones reagent in acetone (25 ml) at −30° C. After the usual work-up, the crude product was charomatographed (hexane: ethyl acetate=5:2) to yield 0.298 g of 13,14-dihydro-15-keto-16R,S-fluoro-11R-(2-tetrahydropyranyl)oxy-PGE$_2$ methyl ester (124).

The methyl ester (124) (0.296 g) was dissolved in a mixed solvent (25 ml) of acetic acid, THF, and water (4:1:2), and the solution was kept at 45° C. for 3 h. Then, a crude product obtained after the usual work-up was chromatographed (benzene - ethyl acetate=2:3) to give 13,14-dihydro-15-keto-16R,S-fluoro-PGE$_2$ methyl ester (125), R=Me.

Yield: 0.202 g.

The n. m. r. spectrum of 13,14dihydro-15-keto- 16-R,S-fluoro-PGE$_2$methyl ester (125) is shown in FIG. 48.

Mass (DI) 384, 366, 346, 335.

EXAMPLE 51 (SEE CHART XIX)

Preparation of
13,14-Dihydro-6,15-diketo-16R,S-fluoro-11R-dehydroxy-11R-methyl-PGE$_1$ ethyl ester (135)

51 - 1) Tosylation of 16R,S-Fluoro-13,14-dihydro-15R,S-(t-butyldimethylsilyl)oxy-PGF$_{2\alpha}$ ethyl ester (126):

Preparation of tosylate (127): 16R,S-Fluoro-13,14-dihydro-15R,S-(t-butyldimethylsilyl)oxy-PGF$_{2\alpha}$ ethyl ester (126) (1.00 g) produced from(−)-Corey lactone (1) and dimethyl(3-fluoro-2-oxoheptyl)phosphonate according to the known method was tosylated with tosyl chloride (4.00 g) in pyridine (10 ml) at 0° C.

Yield: 1.04 g.

51 - 2) Preparation of 16R,S-fluoro-13,14-dihydro-15R,S-(t-butyldimethylsilyl)oxy-PGA$_2$ ethyl ester (128):

The tosylate (127) (1.04 g) was oxidized with Jones reagent (2.67- M, 2 ml) in acetone (30 ml) at −20° C. A crude product obtained after usual processing was chromatographed (hexane-ethyl acetate=5:1) to give 16R,S-fluoro-13,14-dihydro-15R,S-(t-butyldimethylsilyl)oxy-PGA$_2$ ethyl ester (128).

Yield: 0.627 g.

51 - 3) Preparation of 16R,S-Fluoro-13,14-dihydro-11R-dehydroxy-11R-methyl-15R,S-(t-butyldimethylsilyl)oxy-PGE$_2$ ethyl ester (129):

To lithium dimethylcuprate, prepared in ether (70 ml) from copper (I) iodide (1.28 g) and methyl lithium (1.5-M, 9.0 ml) was added an ether solution (40 ml) of the enone (128) (1.114 g). The mixture was stirred for 30 min. Then, after usual processing, there was obtained 16R,S-fluoro-13,14-dihydro-11R-dehydroxy-11R,-methyl-15R,S-t-butyldimethylsilyl)oxy-PGE$_2$ ethyl ester (129).

Yield: 0.931 g.

51 - 4) Preparation of 16R,S-Fluoro-13,14-dihydro-11R-dehydroxy-11R-methyl-15R,S-(t-butyl dimethylsilyl)oxy-PGF$_{2\alpha}$ ethyl ester (130):

The ketone (129) (0.931 g) was reduced with $NaBH_4$ (0.688 g) in methanol (40 ml), and thus 9α-hydroxy-PGF derivative (130) and 9β-hydroxy-PGF derivative (131) were obtained.

The 9β-hydroxy-PGF derivative (131) was oxidized by Jones reagent to the ketone (129), and then reduction of the ketone (129) with $NaBH_4$ was carried out again. A total yield of 0.677 g of 16R,S-fluoro-13,14-dihydro-11R-dehydroxy-11R-methyl-15R,S-(t-butyldimethylsilyl)oxy-PGF$_{2\alpha}$ ethyl ester (130) was obtained.

51 - 5) Preparation of 16R,S-Fluoro-13,14-dihydro-11R-dehydroxy-15R,S-hydroxy-11R-methyl-PGF$_{2\alpha}$ ethyl ester (132):

Tetrabutylammonium fluoride (1.0 - M; 8 ml) was added to a THF solution of 15R,S-(t-butyldimethylsilyl)oxy-PGF$_{2\alpha}$ ethyl ester (130) (0.677 g), and the mixture was stirred at room temperature overnight. A crude product obtained after the usual processing was chromatographed (hexane-ethyl acetate=3:1) to give 16R,S-fluoro-13,14-dihydro-11R-dehydroxy-15R,S-hydroxy-11R-methyl-PGF$_{2\alpha}$ ethyl ester (132) (0.503 g).

51 - 6) Preparation of 13,14-Dihydro-6,15-diketo-16R,S-fluoro-11R-dehydroxy-11R-methyl-PGE$_1$ ethyl ester (135):

The same procedure as in Examples 48 and 49 was followed with using 16R,S-fluoro-13,14-dihydro-11R-dehydroxy-15R,S- hydroxy-11R-methyl-PGF$_{2\alpha}$ ethyl ester (132), and thus there was obtained 13,14-dihydro-6,15-diketo-11R-dehydroxy-11R-methyl-PGE$_1$ ethyl ester (135).

The n. m. r. spectrum of 13,14-dihydro-6,15-diketo-11R-dehydroxy-11R-methyl-PGE$_1$ ethyl ester (135) is shown in FIG. 49.

Mass (DI): 412, 394, 367.

EXAMPLE 52 (SEE CHART XX)

Preparation of
13,14-Dihydro-6,15-diketo-11R-dehydroxy-11R-hydroxymethyl-19-methyl-PGE$_1$ methyl ester (138)

52 - 1) Preparation of 15,15-Ethylenedioxy-13,14-dihidro-11R-dehydroxy-11R-hydroxymethyl-PGE$_2$ methyl ester (137):

15,15-Ethylenedioxy-13,14-dihydro-19-methyl-PGA$_2$ methyl ester (136) (0.410 g) produced from (−)-Corey lactone (1) and dimethyl(6-methyl-2-oxoheptyl)-phosphonate, and 0.255 g of benzophenone were dissolved in 80 ml of methanol. The solution was irradiated through a pyrex filter with a 300 W high pressure mercury lamp. After the ordinary work-up and purification, there was obtained 15,15-ethylene dioxy-13,14-dihidro-11R-dehydroxy-11R-hydroxymethyl-19-methyl-PGE$_2$ methyl ester (137).

52 -2) Preparation of 13,14-Dihydro-6,15-diketo-11R-dehydroxy-11R-hydroxymethyl-19-methyl-PGE$_1$. methyl ester (138):

The same procedure as in Examples 47, 48, and 49 was applied on the compound (137) and thus 13,14-dihydro-6,15-diketo-11R-dehydroxy-11R-hydroxymethyl-19-methyl-PGE$_1$ methyl ester (138) was obtained.

In FIG. 51 there is shown the n. m. r. spectrum of 13,14-dihydro-6,15-diketo-11R-dehydroxy-11R-hydroxymethyl-19-methyl-PGE$_1$ methyl ester (138) is shown in FIG. 50

Mass m/z 410 (M+), 392(M+-18), 379, 361.

EXAMPLE 53 (SEE CHART XXI)

Preparation of 13,14-Dihydro-15-keto-16R,S-fluoro-PGE_2 (140)

53-1) Preparation of 13,14-Dihydro-15-keto-16R,S-fluoro-11R-(2-tetrahydropyranyl)oxy-PGE_2(139):

The carboxylic acid (122) was oxidized in aceton (25 ml) with Jones reagent (2.67-M, 1.1 ml) at −15° C. A crude product obtained after the usual work-up was chromatographed to give 13,14-dihydro-15-keto-16R,S-fluoro-11R-(2-tetrahydropyranyl)oxy-PGE_2 (139). Yield: 0.247 g.

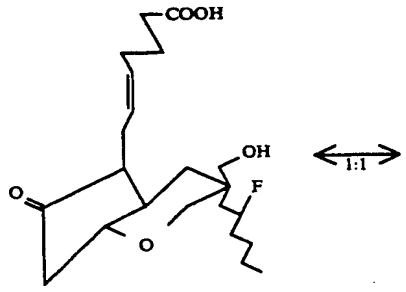
53-2) Preparation of 13,14-Dihydro-15-keto-16R,S-fluoro-PGE_2 (140):

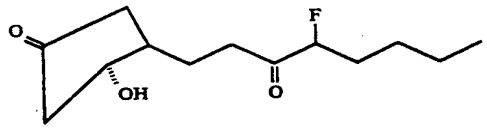
13,14-Dihydro-15-keto-16R,S-fluoro-11R-(2-tetrahydropyranyl)oxy-PGE_2(139) (0.247 g) was dissolved in a mixture (25 ml) of acetic acid - water - THF (4:2:1) to be kept at 45° C. for 3 h. A crude product obtained after the usual work-up was chromatographed to give 13,14-dihydro-15-keto 16R,S-fluoro-PGE_2 (140). Yield: 0.148 g.

The n. m. r. spectrum of 13,14-dihydro-15-keto-16R,S-fluoro-PGE_2 (140) is shown. in FIG. 51.

Mass 352 (M^+-18) 282, 281, 226. C^{13}-n.m.r. was determined using a 400 MHz device. The results are as follows:

Apparent from the above C^{13}-n.m.r. the above compound (140) forms possibly following equilibrium mixture of tautomeric isomers.

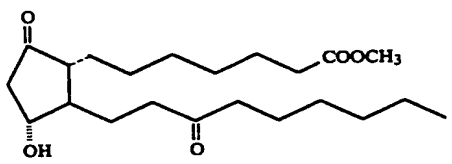




No.	PPM	INT (%)
1	215.845	8.47238
2	213.758	8.04458
3	210.693	5.10931
4	210.460	3.59663
5	210.357	3.26243
6	178.890	8.35974
7	178.700	9.36714
8	131.032	18.77798
9	130.580	16.85946
10	127.135	17.49468
11	126.960	20.51506
12	97.960	4.23425
13	97.799	5.10057
14	97.609	3.64508
15	97.376	4.06103
16	97.171	4.59381
17	96.996	8.52154
18	96.310	5.02938
19	96.208	4.25401
20	95.157	8.06931
21	77.351	98.89423
22	77.030	100.00000
23	76.709	94.29728
24	72.929	19.24167
25	71.294	9.80660
26	71.207	8.76754
27	65.821	3.16846
28	53.999	28.13616
29	53.181	18.97531
30	47.869	24.43601
31	47.051	23.90225
32	45.986	12.52490
33	45.869	12.09867
34	43.753	14.28856
35	35.492	16.17178
36	33.492	2.97718
37	33.230	31.33004
38	31.829	16.02193
39	31.624	16.87059
40	29.858	10.79520
41	29.712	3.99469
42	29.581	11.04714
43	28.866	7.22944
44	28.647	6.83104
45	28.515	7.46747
46	28.297	6.62025
47	27.786	12.35639
48	27.246	9.17236
49	26.662	28.41152
50	26.458	29.42895
51	24.823	29.72020
52	24.575	3.98072
53	24.458	41.26676
54	23.714	16.46572
55	23.655	11.84843
56	22.415	17.92916
57	22.225	34.46823
58	15.175	3.38720
59	13.906	16.04726
60	13.774	23.45338

EXAMPLE 54

Preparation of 13,14-Dihydro-15-keto-20-methyl-PGE_1 methyl ester (141)



(141)

13,14-Dihydro-15-keto-20-methyl-PGE_1 methyl ester (141) was prepared using (−)-Corey lactone together with dimethyl(2-oxooctyl)phosphonate according to the procedure as in Example 41.

The n.m.r. spectrum of the titled compound (141) was shown in FIG. 52.

Mass (DI) m/z 382(M^+), 364, 333.

EXAMPLE 55 (SEE CHART XXII)

Preparation of 13,14-Dihydro-15-keto-Δ^2-PGE_1 methyl ester (146)

According to the same manner as in Example 36 13,14-dihydro-15-keto-Δ^2-PGE_1 methyl ester (146) was prepared using 13,14-dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl)oxy-$PGF_{1\alpha}$ methyl ester (142)

which can be obtained by catalitic hydrogenation of the compound (10).

The n.m.r. spectrum of the titled compound (146) is shown in FIG. 53.

Mass (DI) z/m 366, 348, 316.

EXAMPLE 56 (SEE CHART XXII)

Preparation of 13,14-Dihydro-15-keto-Δ^2-PGE_1 (149)

56-1 Preparation of 13,14-Dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl)oxy-Δ^2-$PGF_{1\alpha}$ (147):

To the solution of 13,14-dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl)oxy-Δ^2-$PGF_{1\alpha}$ methyl ester (144) (0.7687 g) in THF (15 ml) 0.5-M aqueous solution of litium hydroxide (20 ml) was added, and stirred at room temperature over night. A crude carboxylic acid (147) was obtained after a usual work-up. Yield: 0.8779 g.

56-2 Preparation of 13,14-Dihydro-15,15-ethylenedioxy- 11-(2-tetrahydropyranyl)oxy-$\Delta^2PGE_{1\alpha}$ (148):

Carboxylic acid (147) (0.8779 g) was oxidized with Jones reagent (2.67-M, 1.7 ml) at −35° C. in acetone (50 ml). A crude product obtained after a usual work-up was chromatographed (3–5% isopropanol-hexane) to give 13,14-dihydro-15,15-ethylenedioxy-11-(2-tetrahydropyranyl) oxy-Δ^2-PGE_1 (148). Yield: 0.5972 g.

56-3 Preparation of 13,14-Dihydro-15-keto-Δ^2-PGE_1 (149):

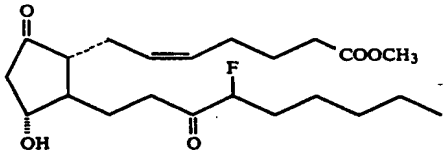
In a mixed solvent of acetic acid:THF:water (3:1:1) (15 ml) Δ^2-PGE_1 (148) (0.5972 g) was dissolved and maintained at 40° C. for 3.5 hours. A crude compound obtained by a usual work-up was chromatographed twice (acid washed Mallincklodt silica-gel, hexane:ethyl acetate=3:1–1:1, and then 8% isopropanol-hexane) to give 13,14-dihydro-15-keto-Δ^2-PGE_1 (149). Yield: 0.2473.

The n.m.r. of the titled compound (149) was shown in FIG. 54.

Mass (DI) z/m 352(M^+), 334, 316.

EXAMPLE 57

Preparation of 13,14-Dihydro-15-keto-16R,S-fluoro-20-methyl-PGE_2 methyl ester (150)



(150)

Using (−)-Corey lactone and dimethyl(3R,S-fluoro-2-oxooctyl)phosphonate, 13,14-dihydro-15-keto-16R,S-fluoro-20-methyl-PGE_2 methyl ester (150) was prepared according to the same manner as in Example 50.

The n.m.r. spectrum of the titled compound (150) was shown in FIG. 55.

Mass (DI) m/z 398(M^+), 380.

EXAMPLE 58 (SEE CHART XXIII)

Preparation of 13,14-Dihydro-15-keto-16,16-difluoro-PGE_2 methyl ester (160):

58-1 Preparation of 1S-2-Oxa-3-oxo-6R-(4,4-difluoro-3-oxo-trans-1-octenyl)-7R-(4-phenylbenzoyl)oxy-cis-bicyclo(3,3,0)octane (151):

Aldehyde (2) was obtained by the oxidation of (−)-Corey lactone (1) (6.33 g) with Collins reagent. Separately thallium ethoxide (4.26 g) was dissolved in benzene, to which the solution of dimethyl(3,3-difluoro-2-oxoheptyl)phosphonate (4.64 g) in benzene was added at cool temperature, and the mixture was stirred for 30 min. To the resultant the solution of the aldehyde (2) in benzene as prepared above was added, and stirred at room temperature for 3 h. After the mixture was neutralized with acetic acid, a saturated aqueous solution of potassium iodide was added and passed through a celite column. After a usual work-up the desired unsaturated ketone (151) was obtained. Yield: 3.88 g.

58-2 Preparation of 1S-2-Oxa-3-oxo-6R-(4,4-difluoro-3R,S-hydroxy-1-octyl)-7R-(4-phenylbenzoyl)oxy-cis-bicyclo(3,3,0)octane (153):

The unsaturated ketone (151) (3.88 g) was hydrogenated with palladium on carbon (5%) in ethyl acetate (40 ml) to give the saturated ketone (152). The saturated ketone (152) was reduced with $NaBH_4$ in a mixed solvent of methanol-THF (70:30) to give the alcohol (153). Yield: 4.02 g.

58-3 Preparation of 1S-2-Oxa-3-oxo-6R-(4,4-difluoro-15R,S-t-butyldimethylsilyloxy-1-octyl)-7R-hydroxy-cis-bicyclo(3,3,0)octane (155):

The alcohol (153) was treated with imidazol and t-butyldimethylsilyl chloride in DMF to give 1S-2-oxa-3-oxo-6R-(4,4-difluoro-15R,S-t-butyldimethylsilyloxy-1-octyl)-7R-(4-phenylbenzoyl)oxy-cis-bicyclo(3.3.0) octane (154). The resultant (154) was methonolysised with potassium carbonate (1.14 g) in methanol (20 ml) to give 1S-2-oxa-3-oxo-6R-(4,4-difluoro-15R,S-t-butyldimethylsilyloxy-1-octyl)-7R-hydroxy-cis-bicyclo(3,3,0) octane (155). Yield: 2.89 g.

58-4 Preparation of 1S-2-Oxa-3-oxo-6R-(4,4-difluoro-15R,S-t-butyldimethylsilyloxy-1-octyl)-7R-(2-tetrahydropyranyl)oxy-cis-bicyclo(3,3,0)octane (156):

The alcohol (155) was converted to the tetrahydropyranyl ether (156) according to a known method. Yield: 3.38 g.

58-5 Preparation of 16,16-difluoro-13,14-dihydro-15R,S-t-butyldimethylsilyloxy-11-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ methyl ester (157):

The desired silylether (157) was obtained from the tetrahydropyranyl ether (156) (3.38 g) according to the procedure in Examples 50 and 51. Yield: 3.02 g.

58-6 Preparation of 16,16-Difluoro-13,14-dihydro-15R,S-hydroxy-11R-(2-tetrahydropyranyl)oxy-$PGF_{2\alpha}$ methyl ester (158):

The silyl ether (157) (0.882 g) was treated with tetrabutylammonium fluoride (1.1-M, 10.6 ml) in THF (25 ml) to give the desired diol (158). Yield: 0.710 g.

58-7 Preparation of 13,14-Dihydro-15-keto-16,16-difluoro-PGE_2methyl ester (160):

Collins reagent was prepared from chromic anhydride (2.57 g) and pyridine (4.15 nil) in dichloromethane (40 ml). To the resultant was added the solution of the diol (158) (0.360 g) in dichloromethane (15 ml). After the usual work-up and purification, 13,14-dihydro-15-keto-16,16-difluoro-11-(2-tetrahydropyranyl)oxy-PGE_2methyl ester (159) was obtained. Yield: 0.277 g. The obtained compound (159) (0.208 g) was dissolved in a mixed solvent of acetic acid: THF:water (4:2:1) (30 ml) and maintained at 45° C. for 3.5 h. A crude compound obtained after a usual work-up was chromatographed to give 13,14-dihydro-15-keto-16,16-difluoro-PGE_2 methyl ester (160). Yield: 0.208 g.

The n.m.r. spectrum of the titled compound (160) is shown in FIG. 56.

Mass (DI) z/m 402(M+), 384(M+-18), 364.

EXAMPLE 59 (SEE CHARTS XXIV AND XXV)

Preparation of 13,14-dihydro-15-keto-5,6-dehydro-20-methoxy-PGE_2 methyl ester (141)

To a solution of 8-methoxy-3,3-ethylenedioxy-1-iodooctane (167) (0.985 g) in ether (15 ml) t-butyllitium (2.3-M, 2.87 ml) was added dropwise at −78° C., and the resultant mixture was stirred for 3 h, to which an ether solution of copper (I) iodide and tributylphosphine was added all at once, and stirred for 20 min. To the reaction mixture was added a solution of 4R-t-butyldimethylsilyloxy-2-cyclopentene-1-on (168) (0.637 g) in THF (21 ml) dropwise over 15 min. After 15 min HMPA (2.61 ml) was added to the resultant followed by the addition of triphenyltin chloride (1.217 g) in THF (6 ml) after 30 min, and then stirred for 15 min. The reaction mixture was cooled at −30° C., to which a solution of 6-carboxymethoxy-1-iodo-2-hexyne (169) (3.19 g) in HPMA (2.61 ml) was added, and stirred for 4.5 h and then at room temperature for 12 h. The reaction mixture was poured into a saturated ammonium chloride solution with vigorous agitation. The organic layer was collected. The aqueous layer was extracted with ether, and the extracted layer was put together with the organic layer, which was then washed with a saturated aqueous solution of sodium chloride. After dried the organic layer was concentrated under reduced pressure to give a crude product. The crude product was chromatographed to give 11-t-butyldimethylsilyloxy-15,15-ethylenedioxy-13,14-dihydro-5,6-dehydro-20-methoxy-PGE_2 methyl ester (170). Yield: 0.3700 g.

n.m.r.: 0.08(3H,s), 0.10(3H,s), 1.3–2.8(24H, m), 3.30 (3H,s), 3.32(2H,t), 3.74(3H,s), 3.90(4H,s), 4.10(1H,m).

59-2 Preparation of 13,14-dihydro-15-keto-5,6-dehydro-20-methoxy-PGE_2 methyl ester (171):

A mixture (3 ml) of hydrofluoric acid (46%): acetonitrile (1:2) cooled at 0° C. was added to 11-t-butyldimethylsilyloxy-15,15-ethylenedioxy-13,14-dihydro-5,6-dehydro-20-methoxy-PGE_2 methyl ester (170) (0.035 g), and stirred at room temperature for 25 min, to which water was poured, and the reaction product was extracted with ethyl acetate. The obtained organic layer was neutralized with a saturated aqueous solution of sodium bicarbonate, and concentrated under reduced pressure to give a crude product, which was chromatographed to give 13,14-dihydro-15-keto-5,6-dehydro-20-methoxy-PGE_2 methyl ester (171). Yield: 0.0081 g.

The n.m.r. spectrum of the obtained compound (171) was shown in FIG. 57.

EXAMPLE 60 (SEE CHART XXVI)

Preparation of 13,14-dihydro-15-keto-16R,S,16R,S-difluoro-PGE_2(174)

60-1 synthesis of 13,14-dihydro-15R,S-hydroxy-11R-(2-tetrahydropyranyl)oxy-16,16-difluoro-PGE_2 (172):

13,14-dihydro-15R,S-hydroxy-11R-(2-tetrahydropyranyl)oxy-16,16-difluoro-PGE_2 methyl ester (158) (0.731 g) was dissolved in sodium hydroxide:methanol (1:3) solution (60 ml), and stirred at room temperature for 5 hours. The resultant was treated by a usual work-up to give a crude carbonylic acid (172). Yield: 0.722 g.

60-2 synthesis of 13,14-dihydro-15-keto-16,16-difluoro-PGE_2 (174):

The title compound (174) was prepared according to the same manner as the process 58-7 in the Example 58 excepting using the compound (172) (0.722g) instead of the compound (158). Yield: 0.192 g.

The n.m.r. spectrum of the title compound (174) is as follows: ^1H NMR (200 MHz, $CDCl_3$) δ0.93 (3H, t, J=7.1 Hz), 1.23–2.98 (22H, m), 4.11–4.28 (1H, m C(11)H), 5.34–5.48 (2H, m).

Mass (m/z) 388 (M+), 370 (M+-H_2O).

Existence of the hemiacetal is confirmed by C^{13} n.m.r. spectrum of the compound (174).

The n.m.r. data of compounds in the above Examples are shown as follows, wherein the compounds number in brackets.

(6) δ: 0.88 (3H, 6 Hz), 1.1–3.0(19H, m), 3.8–4.1(1H, m), 3.90(4H, s), 4.93(1H, dt, J=6 Hz, J=3 Hz)

(7) 0.88(3H, 6 Hz), 1.0–2.9(24H, m), 350(1H, m), 3.88(4H, s), 3.6–4.1(2H, m), 4.63(1H, bs), 4.8–5.06(1H, m)

(11) 0.88(3H, t, J=6 Hz), 1.24(3H, t, J=7.5 Hz), 1.0–2.7(30H, m), 3.3–3.6(1H, m), 3.89(4H, s), 3.6–4.35(5H, m), 4.10(2H, q, 8.75 Hz), 4.35–4.7(1H, m)

(23) 0.7–1.0(6H, m), 1.0–3.0(18H, m), 3.8–4.1(1H), 3.90(4H, s), 4.92(1H, dt, J=6 Hz, J=3 Hz)

(30) 0.73–1.0(6H, m), 1.24(3H, t, J=7 Hz), 1.0–2.5(29H, m), 3.3–4.7(7H, m), 3.88(4H, s), 4.11(2H, q, J=7 Hz)

(38) 0.88(3H, t, J=6 Hz), 1.1–3.6(16H, m), 4.43(0.5H, t, J=6 Hz), 4.9–5.3(2.5H, m), 7.3–8.2(9H, m)

(39) 0.90(3H, t, J=6 Hz), 1.1–3.2(17H, m), 3.3–3.8(1H, m), 3.8–4.16(0.5H, m), 4.33–4.75(0.5H, m), 4.9–5.16(1H, bs), 5.16–5.33(1H, m), 7.3–8.2(9H, m)

(40) 0.07(6H, S), 0.87(9H, S), 0.7–1.05(3H), 1.05–3.2(16H, m), 3.5–3.85(1H, m), 3.85–4.15(0.5H, m), 4.3–4.6(0.5H, m), 4.95–5.15(1H, m) 5.15–5.33(1H, m), 7.3–8.2(9H, m)

(41) 0.07(6H, s), 0.88(9,H, S), 0.75–1.05(3H), 1.05–3.0(17H, m), 3.45–3.85(1H, m), 3.85–4.15(1.5H, m), 4.4–4.65(0.5H, m), 4.93(1H, dd, J=6 Hz, J=3 Hz)

(42) 0.05(6H, s), 0.88(9H,s), 0.75–1.05(3H), 1.05–3.0(22H, m), 3.3–5.1(7H, m)

(45) 0.07(6H, s), 0.88(9H, S), 0.75–1.0(3H), 1.23(3H, t, J=7 Hz), 1.05–2.6(29H, m), 3.2–4.7(7H, m), 4.07(2H, q, J=7Hz), 5.1–5.65(2H, m)

(46) 0.88(3H, t, J=6 Hz), 1.23(3H, t, J=7 Hz), 1.1–2.6(30H, m), 3.3–4.2(6H, m), 4.10(2H, q, J=7 Hz), 4.60(1H, bS), 5.1–5.7(2H, m)

(47) 0.90(3H, t, J=6Hz), 1.25(3H, t, J=6 Hz), 1.03–2.70(29H, m), 3.25–4,70(9H, m), 4.07(2H, q, J=6 Hz)

(52) 0.92(3H, t, J=6 Hz), 1.24(3H, t, J=6 Hz), 1.05–2.75(21H, m), 3.3–3.8(1H, m), 4.10(2H, q, 6 Hz), 4.10(0.5H), 4.4–4.7(0.5H, m), 5.67(2H, m), 6.10(1H, dd, J=6 Hz, J=3Hz), 7.57(1H, dd, J=6 Hz, J=3Hz)

(92) 0.88(3H, t, J=6Hz), 1.1–1.8(16H, m), 2.2–3.0(4H, m), 3.88(4H, s), 5.4–5.57(1H, m), 5.80(1H, dd, J=6 Hz, J=3 Hz), 6.02(1H, dd, J=6 Hz, 3Hz)

(95) 0.88(3H, t, J=6Hz), 1.0–2.6(27H, m), 3.62(3H, s), 3.88(4H, S), 4.5–4.7(1H, m), 5.1–5.6(2H, m), 5.6–6.0(2H, m)

(96) 0.87(3H, t, J=6 Hz), 1.1–2.7(26H, m), 3.62(3H, S), 3.87(4H, S), 5.15–5.60(2H, m), 6.07(1H, dd, J=6 Hz, J=3 Hz), 7.53(1H, dd, J=6 Hz, J=3 Hz)

(97) 0.87(3H, t, J=6Hz), 1.10(3H, d, J=5Hz), 1.0–2.7(29H, m), 3.62(3H, S), 3.7–4.0(4H), 5.1–5.6(2H, m)

(104) 0.7–1.03(6H, m), 1.03–2.6(34H, m), 3.3–4.3(6H, m), 3.88(4H, S), 4.08(2H, q, J=7Hz), 4.60(1H, m)
(112) 0.88(3H, t, J=6 Hz), 0.97(3H, d, J=6 Hz), 1.23(3H, t, J=7Hz), 1.1–2.5(25H, m), 3.90(4H, s), 4.10(2H, q, J=7 Hz), 3.8–4.7(3H, m)
(118) 0.90(3H, t, J=6 Hz), 1.1–3.1(17H, m), 3.93(1H, q, J=6 Hz), 4.41(0.5H, t, J=6 Hz), 4.7–5.1(1.5H, m)
(127) 0.05(6H, s), 0.88(9H, s), 0.75–1.0(3H), 1.23(3H, t, J=7 Hz), 1.05–2,4(23H, m), 2,42(3H, s), 4.08(2H, q, J=7 Hz), 3.9–4.7(4H, m), 5.35(2H, m), 7.27(2H, d, J=9 Hz), 7.75(2H, d, J=9 Hz)
(129) 0.05(6H, s), 0.88(9H, s), 0.7–1.0(3H), 1.23 (3H, t, J=7 Hz), 1.05–2.65(20H, m), 3.4–3.85(1H, m), 4.07(2H, q, J=7Hz), 3.85–4.15(0.5H), 4.35–4.65(0.5H, m) 5.35(2H, m), 6.08(1H, dd, J=6Hz, J=3Hz), 7.53(1H, dd, J=6 Hz, J=3 Hz)
(137) 0.85(6H, d, J=7 Hz), 1.0–2.7(25H, m), 3.62(3H, S), 3.5–3.75(2H), 3.88(4H, s), 5.1–5.6(2H, m)

The above data were determined by n.m.r. measuring apparatus R-90H available from Hitachi Seisakusho.

TEST EXAMPLE 1

Antiulcer Activity

As test samples, we used the PGE as obtained in Examples 2 to 52 as described herein, 13,14-dihydro-15-keto-PGE $_2$ (produced by Funakoshi & Co.) being employed as control reference.

Each group of test animals used consisted of 8 to 10 male rats of the Crj: Wistar strain, weighing 180 to 230 g. Test animals were fasted for 24 hours before the oral administration of the test samples; in the case of development of confinement-stress induced ulcers through immersion in water, 10 minutes after oral administration of the test specimens, the animals were confined in a stress cage developed by Univ. of Tokyo, then immersed up to the ensiform process of sternum in water at 23° C. for 4 hours and sacrificed; in the case of formation of indomethacin-induced ulcers, shortly after the materials were given, animals were given indomethacin orally at a dose of 10 mg/kg and sacrificed after 5 hours.

The stomacks were taken out, followed by fixation with 1% formalin, and incised along the greater curvature to carry our investigation under an illuminated magnifier for ulceration. The degree and extent of lesion and ulcer were rated based on the ulceration index being classified into the following five numerical categories:

0: normal, with no lesion detected;
1: bleeding or erosion of mucosa;
2: development of less than 5 small ulcers (not greater than 2 mm in diameter);
3: generation of not less than 5 small ulcers or a large ulcer (not less than 2 =in diameter);
4: generation of not less than 2 large ulcers.

On the basis of the criteria that the rats with the ulceration index of not less than, "2", the ulcer inhibition rate (ED_{50}) was calculated from ulcer-generation ratio in the control and the ratio in the test specimens.

The results are shown in Table 1 (confinement-stress induced ulcers through immersion in water) and Table 2 (indomethacin-induced ulcers).

TABLE-1

(Hydrorestraint Stress Ulcer Preventing Effect)

Material tested	Dosage (mg/kg)	Animal used (no. of heads)	Ulcer index (aver. ± SE)	Inhibition factor (%)	ED_{50} (mg/kg)
Control	—	10	3.0 ± 0.2	—	—
(1)	20	8	2.5 ± 0.3	6.3	>20
(2)	15	8	0.5 ± 0.3	87.5	4.0
	5	8	1.4 ± 0.4	58.3	
(3)	10	8	0.3 ± 0.1	100.0	
	3	8	1.1 ± 0.3	86.1	1.5
	1	8	2.1 ± 0.4	25.0	
(4)	5	8	1.6 ± 0.3	44.4	7.0
	1	8	2.1 ± 0.4	16.7	
(5)	5	8	1.5 ± 0.3	44.0	6.5
	1	8	2.2 ± 0.4	14.3	
(6)	10	8	1.4 ± 0.2	72.2	5.5
	3	8	2.4 ± 0.3	28.0	
(7)	10	8	1.1 ± 0.2	75.0	4.5
	3	8	1.9 ± 0.3	37.5	
(8)	1	10	1.5 ± 0.5	62.5	0.60
	0.3	10	2.0 ± 0.3	30.6	
(9)	1	10	1.5 ± 0.3	75.0	0.45
	0.3	10	1.9 ± 0.2	37.5	
(10)	3	10	0.9 ± 0.4	78.4	1.5
	1	10	2.0 ± 0.4	25.5	
(11)	10	10	1.1 ± 0.2	85.7	
	3	10	1.4 ± 0.2	57.1	2.4
	1	10	2.0 ± 0.4	25.0	
(12)	10	10	1.1 ± 0.2	75.3	6.2
	3	10	2.6 ± 0.3	13.6	
(13)	10	8	1.5 ± 0.4	50.0	10
	3	8	2.6 ± 0.3	13.2	
(14)	1	10	1.3 ± 0.2	77.8	
	0.3	10	1.7 ± 0.3	44.4	0.35
	0.1	10	1.9 ± 0.4	22.2	
(15)	6	10	0.8 ± 0.3	79.9	3.5
	3	10	1.8 ± 0.3	37.5	
(16)	1	10	1.7 ± 0.3	44.4	2.0
	0.3	10	2.5 ± 0.3	0	
(17)	0.1	10	0.5 ± 0.2	95.7	
	0.03	10	1.5 ± 0.3	81.4	0.005
	0.01	10	1.7 ± 0.2	67.1	
	0.003	10	2.2 ± 0.4	39.0	
(18)	0.3	10	0.5 ± 0.2	95.9	
	0.1	10	0.7 ± 0.2	89.0	0.03
	0.03	10	1.7 ± 0.3	49.3	
(19)	0.3	10	1.1 ± 0.2	83.3	
	0.1	10	1.6 ± 0.3	63.0	0.06
	0.03	10	2.5 ± 0.4	33.3	
(20)	3	10	0.9 ± 0.2	87.7	
	1	10	1.7 ± 0.2	58.3	0.80
	0.3	10	2.4 ± 0.3	22.2	
(21)	3	10	0.9 ± 0.2	87.5	0.80
	1	10	1.6 ± 0.3	52.4	
(22)	3	10	1.2 ± 0.3	70.0	1.8
	1	10	2.0 ± 0.4	30.0	
(23)	3	10	2.0 ± 0.2	50.0	3.0
	1	10	2.9 ± 0.3	12.5	
(24)	10	10	1.4 ± 0.2	87.1	2.0
	3	10	1.7 ± 0.2	61.4	
(25)	10	8	1.4 ± 0.2	62.5	8.0
	3	8	2.3 ± 0.4	12.5	
(26)	10	8	1.1 ± 0.2	72.2	4.0
	3	8	1.6 ± 0.3	44.4	
(27)	6	8	1.6 ± 0.2	56.0	5.0
	3	8	2.1 ± 0.3	31.8	
(28)	6	8	1.3 ± 0.3	70.2	4.0
	3	8	1.9 ± 0.2	36.0	
(29)	6	10	2.0 ± 0.4	42.2	>6
	3	10	2.5 ± 0.3	30.0	
(30)	6	8	1.1 ± 0.2	57.8	5.0
	3	8	2.3 ± 0.4	29.7	
(31)	0.3	10	1.0 ± 0.2	75.0	
	0.1	10	2.2 ± 0.3	37.5	0.14
	0.03	10	2.6 ± 0.4	12.5	
(32)	1	10	0.8 ± 0.2	82.3	
	0.3	10	1.5 ± 0.3	57.0	0.2
	0.1	10	2.0 ± 0.4	27.9	
(33)	5	10	1.2 ± 0.3	55.0	3.9
	1	10	2.6 ± 0.3	25.0	

TABLE-1-continued

(Hydrorestraint Stress Ulcer Preventing Effect)

Material tested	Dosage (mg/kg)	Animal used (no. of heads)	Ulcer index (aver. ± SE)	Inhibition factor (%)	ED_{50} (mg/kg)
(34)	10	10	0.8 ± 0.3	90.0	
	3	10	1.4 ± 0.4	60.0	1.3
	1	10	2.0 ± 0.4	40.0	
(35)	3	10	1.2 ± 0.3	77.5	
	1	10	1.5 ± 0.3	55.0	0.9
	0.3	10	2.3 ± 0.3	21.3	
(36)	1	10	1.5 ± 0.3	57.0	0.8
	0.3	10	2.4 ± 0.4	22.6	
(37)	6	10	1.0 ± 0.2	79.7	
	3	10	1.9 ± 0.2	45.9	3.0
	1	10	2.7 ± 0.4	8.1	
(38)	3	10	1.0 ± 0.2	79.7	
	1	10	1.9 ± 0.2	45.9	1.5
	0.3	10	2.7 ± 0.4	8.1	
(39)	3	10	0.7 ± 0.2	85.3	
	1	10	1.0 ± 0.2	77.5	0.4
	0.3	10	2.0 ± 0.3	30.2	

TABLE-2

(Indomethacin Ulcer Preventing Effect)

Material tested	Dosage (mg/kg)	Animal used (no. of heads)	Ulcer index (aver. ± SE)	Inhibition factor (%)	ED_{50} (mg/kg)
Control	—	10	2.5 ± 0.3	—	—
(1)	20	8	2.4 ± 0.4	4.0	>20
(2)	20	9	0.4 ± 0.2	100.0	
	6	8	1.4 ± 0.3	50.0	6.0
	3	8	1.9 ± 0.4	30.0	
(3)	10	9	1.0 ± 0.3	71.4	4.4
	3	9	1.7 ± 0.4	42.9	
(8)	3	10	1.7 ± 0.3	42.9	3.8
	1	10	2.3 ± 0.4	14.3	
(9)	3	10	1.5 ± 0.3	50.5	3.0
	1	10	2.1 ± 0.3	37.5	
(11)	10	10	2.0 ± 0.2	50.0	10.0
	3	10	2.6 ± 0.3	0	
(12)	10	10	0.8 ± 0.2	71.4	7.4
	3	10	1.6 ± 0.3	48.0	
(14)	3	10	0.6 ± 0.1	80.0	1.5
	1	10	2.0 ± 0.3	32.0	
(16)	10	10	1.0 ± 0.2	60.0	8.2
	3	10	2.3 ± 0.3	10.0	
(18)	1	10	0.2 ± 0.02	100.0	
	0.3	10	1.4 ± 0.1	62.5	0.17
	0.1	10	1.8 ± 0.2	38.3	
(19)	10	10	0.4 ± 0.1	85.7	3.6
	3	10	1.9 ± 0.2	42.9	
(20)	10	10	0.6 ± 0.1	87.5	3.5
	3	10	1.3 ± 0.2	44.4	
(21)	10	10	1.5 ± 0.3	80.0	6.0
	3	10	2.5 ± 0.4	0	
(23)	10	10	1.5 ± 0.3	50.0	10.0
	3	10	2.0 ± 0.3	25.0	
(30)	10	10	0.6 ± 0.1	71.5	
	3	10	2.1 ± 0.4	24.0	0.9
	1	10	2.4 ± 0.5	10.0	
(33)	10	10	1.6 ± 0.2	62.0	6.3
	3	10	2.3 ± 0.3	30.0	
(34)	10	10	1.9 ± 0.2	70.0	6.0
	3	10	2.2 ± 0.4	20.0	
(35)	10	10	1.0 ± 0.2	72.5	4.8
	3	10	2.3 ± 0.4	29.3	

Materials tested in Table 1 is shown hereinafter:

(1) 13, 14-dihydro-15-keto-PGE_2,
(2) 13, 14-dihydro-15-keto-PGE_2 methyl ester,
(3) 13, 14-dihydro-15-keto-PGE_2 ethyl ester,
(4) 13, 14-dihydro-15-keto-PGE_2-n-propyl ester,
(5) 13, 14-dihydro-15-keto-PGE_2 isopropyl ester,
(6) 13, 14-dihydro-15-keto-PGE_1 methyl ester,
(7) 13, 14-dihydro-15-keto-PGE_1 ethyle ester,
(8) 13, 14-dihydro-6,15-diketo-PGE_1 methyl ester,
(9) 13, 14-dihydro-6,15-diketo-PGE_1 ethyl ester,
(10) 13, 14-dihydro-6,15-diketo-PGE_1n-butyl ester,
(11) (±)13, 14-dihydro-6,15-diketo-PGE_1 ethyl ester,
(12) 13, 14-dihydro-15-keto-3R,S-methyl-PGE_2 methyl ester,
(13) 13, 14-dihydro-15-keto-3R,S-methyl-PGE_2 ethyl ester,
(14) 13, 14-dihydro-15-keto-16R,S-fluoro-11-dehydroxy-11R-methyl-PGE_2 ethyl ester,
(15) 13, 14-dihydro-15-keto-11-dehydroxy-11R-methyl-PGE_2 ethyl ester,
(16) 13, 14-dihydro-15-keto-16R,S-hydroxy-PGE_2 ethyl ester,
(17) 13, 14-dihydro-15-keto-16R,S-fluoro-PGE_2,
(18) 13, 14-dihydro-15-keto-16R,S-fluoro-PGE_2 methyl ester,
(19) 13, 14-dihydro-15-keto-16 R,S-fluoro-PGE_2 ethyl ester,
(20) 13, 14-dihydro-15-keto-16R,S-methyl-PGE_2 methyl ester,
(21) 13, 14-dihydro-15-keto-16R,S-methyl-PGE_2 ethyl ester,
(22) 13, 14-dihydro-15-keto-3R,S,16R,S-dimethyl-PGE_2 methyl ester,
(23) 13, 14-dihydro-15-keto-19-methyl-PGE_2 methyl ester,
(24) 13, 14-dihydro-15-keto-19-methyl-PGE_2 ethyl ester,
(25) 13, 14-dihydro-15-keto-20-isopropylidene-PGE_2 methyl ester,
(26) 13, 14-dihydro-15-keto-20-ethyl-PGE_2 methyl ester,
(27) 13, 14-dihydro-15-keto-20-ethyl-PGE_2 ethyl ester,
(28) 13, 14-dihydro-15-keto-20-ethyl-11-dehydroxy-11R-methyl-PGE_2 methyl ester,
(29) 13, 14-dihydro-15-keto-20-n-propyl-PGE_2 methyl ester,
(30) 13, 14-dihydro-15-keto-20-ethyl-PGE_1 methyl ester,
(31) 13, 14-dihydro-6,15-diketo-16R,S-fluoro-PGE_1 ethyl ester,
(32) 13, 14-dihydro-6,15-diketo-16R,S-fluoro-11-dehydroxy-11R-methyl-PGE_1 ethyl ester,
(33) 13, 14-dihydro-6,15-diketo-16R,S-methyl-PGE_1 methyl ester,
(34) 13, 14-dihydro-6,15-diketo-16R,S-methyl-PGE_1 ethyl ester,
(35) 13, 14-dihydro-6,15-diketo-19-methyl-PGE_1 methyl ester,
(36) 13, 14-dihydro-6, 15-diketo-19-methyl-PGE_1 ethyl ester,
(37) 13, 14-dihydro-6, 15-diketo-20-methyl-PGE_1 ethyl ester,
(38) 13, 14-dihydro-6, 15-diketo-11-dehydroxy-11R-methyl-PGE_1 methyl ester,
(39) 13,14-dihydro-6,15-diketo-11-dehydroxy-11R-methyl-PGE_1ethyl ester.

From the foregoing results, it can be seen that while 13, 14-dihydro-15-keto-PGE_2, as a physiologically and pharmacologically inactive metabolite, shows no antiulcerative effect, it can have antiulcerative effect if it is made into an ester compound of 13, 14-dihydro-15-keto-PGE or a compound similar thereto.

TEST EXAMPLE 2

The following 4 materials were measured as to their respctive effects of ulcer prevention, intestinal constriction, tracheorelaxation, and uteroconstriction, and examined in comparison to one another. The results are shown in Table 3.

TABLE-3

Material tested	Ulcer inhibiting effect ED_{50} (mg/kg)	Intestinal constriction effect	Trachael relaxation effect	Uterus constriction effect
A	0.5	+	+	+
B	0.4	+	+	±
C	>20	−	±	±
D	1.5	−	−	−

Materials tested:
A: PGE_2 (product of Funakoshi Yakuhin K.K.)
B: PGE_2 ethyl ester (produced by Applicant Co.)
C: 13, 14-dihydro-15-keto-PGE_2 (product of Funakoshi Yakuhin K.K.)
D: 13, 14-dihydro-15-keto-PGE_2 ethylester

(1) Antiulcerative Effect

The procedure of Test Example 1 was followed in determining values for hydrorestraint stress-ulcer preventing effect in terms of ED_{50}.
++: alvin flux developed at a concentration lower than 1 mg/kg;
+: alvin flux developed at concentrations of 1~10 mg/kg;
−: no flux developed at a concentration higher than 10 mg/kg.

(2) Intestinal Constriction Effect

A male Wister rat (of 250~300 g in weight) was struck to death, and immediately its carotid artery was cut to dehematize. An ileum portion located about 10 cm from the cecum was extracted, and after its contents were washed away with a Tyrode liquid, a 1.5~2 cm long part of it was cut off and hung in a Magnus tube.

The constriction of the ileum was brought to rest for 15~20 minutes until the ileum was allowed to be stabilized, and subsequently the ileum was constricted with 10^{-6} g/ml of acetylcholine. After constrictions of same magnitude were had two times, the material to be tested was cumulatively administered at one-minute intervals.

Constrictions with the material tested were expressed in terms of ratios, based on constriction per 10^{-6} g/ml of acetylcholine, and values for ED_{50} were determined.
+: $ED_{50} < 10^{-6}$ M
±: 10^{-4} M ≦ ED_{50} ≦ 10^{-6} M
−: 10^{-4} M < ED_{50}

(3) Tracheal Relaxation

A male gunea pig (of about 300 g in weight) was struck to death, and its artery was cut to dehematize. Its trachea, after having been extracted, was cut open lengthwise on the opposite side to the trachea smooth muscle, and seven tracheal rings were connected by string in a chain-like pattern, same being hung in a Magnus tube.

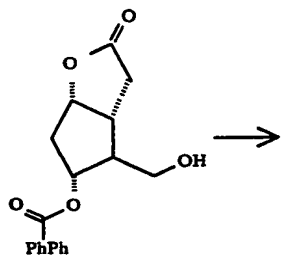
Trachea was brought to rest for 60~90 minutes and until tracheal equilibrium was reached. Thereafter, 5.4×10^{-4} M of histamine was administered in such manner that it was cumulatively administered at 6 minutes' intervals after a constriction peak was reached. Tracheal relaxation with the material tested was expressed in terms of ratio of constrictional inhibition under histamine administering, and values for IC_{50} were determined.
+: $IC_{50} < 10^{-7}$ M
±: 10^{-5} M ≦ IC_{50} ≦ 10^{-7} M
−: 10^{-5} M < IC_{50}

(4) Uterine Constriction

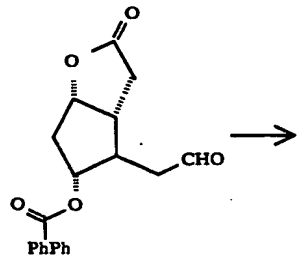
A female rat (of 150 g in weight) was dehematized to death, and its uterus was taken out, which was cut to a length of 1.5–2.5 cm. The cut uterus was hung in a magnus tube. The uterus was constricted several times with 1 mU Oxytocin. After stable uterine movement was obtained, the material to be tested was independently administered. Constrictions with the material were expressed in terms of ratios based on constriction by 1 mU of oxytocin = 100, and values for EC_{50} were determined on the following standards.
+: $EC_{50} < 10^{-7}$ M
±: 10^{-5} M ≦ EC_{50} ≦ 10^{-7} M
−: 10^{-5} M < EC_{50}

From the results of the foregoing tests it can be seen that PGE_2 and PGE_2 ethylester can, in addition to their ulcer inhibiting effects, concurrently produce intestinal constriction, tracheal relaxation, and uterus constriction. Whilst, no pharmacological or physiological effect, such as ulcer inhibiting effect, can be found with 13,14-dihydro-15-keto-PGE_2. However, it can be recognized that 13,14-dihydro-15-keto-PGE_2 ethylester, an ester compound of said 13, 14-dihydro-15-keto-PGE_2, can produce a high degree of ulcer inhibiting effect, though it has no such effet as intestinal, uterus constriction, tracheal relaxation and the like.

Chart 1



1



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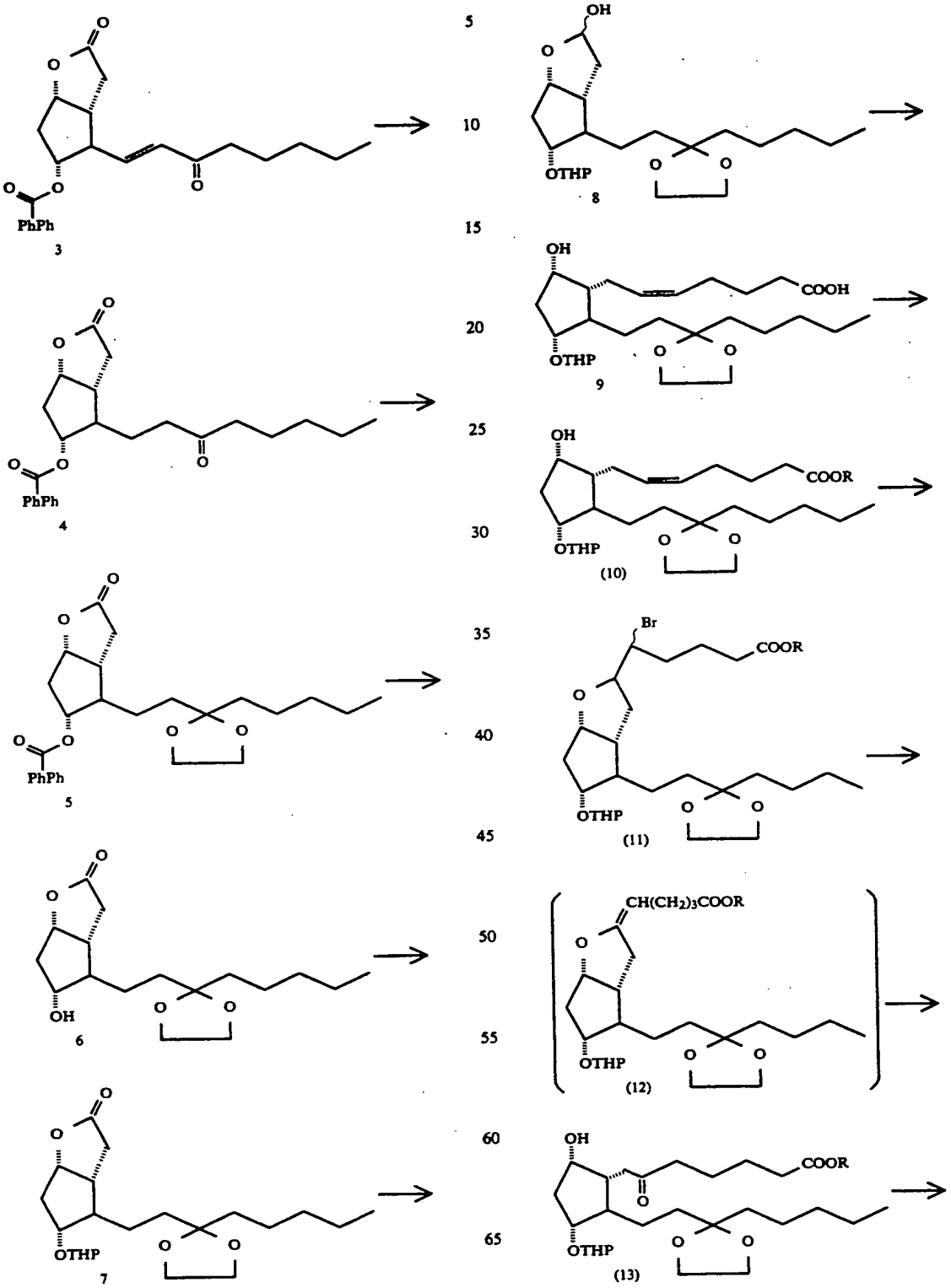

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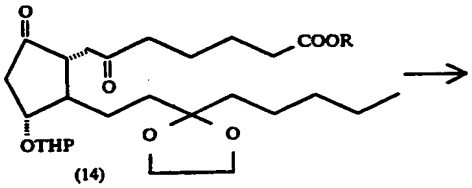

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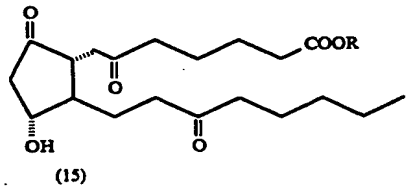

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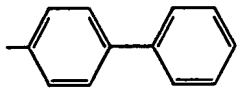

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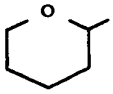

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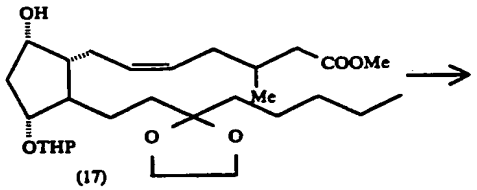

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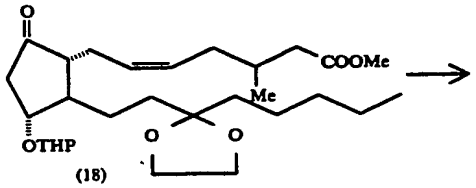

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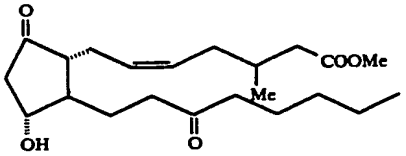

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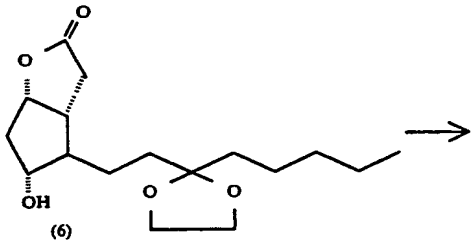

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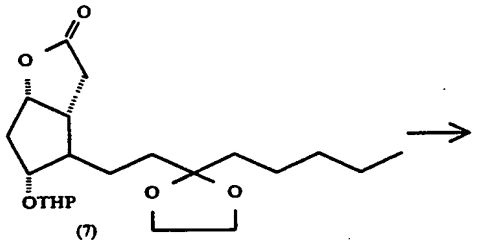

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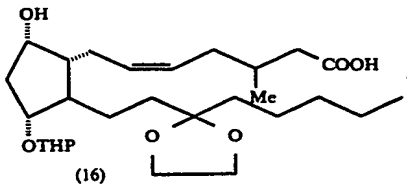

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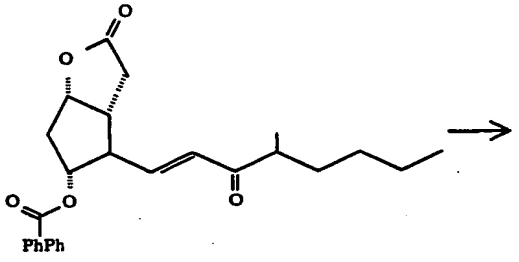

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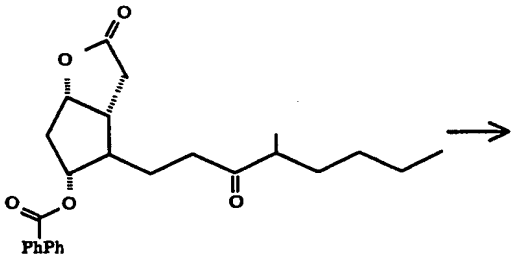

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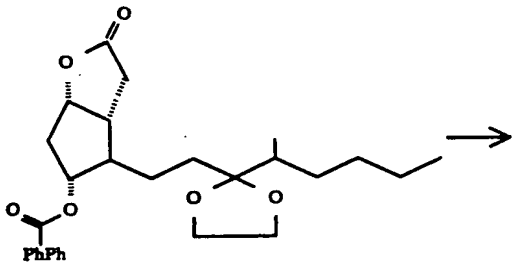

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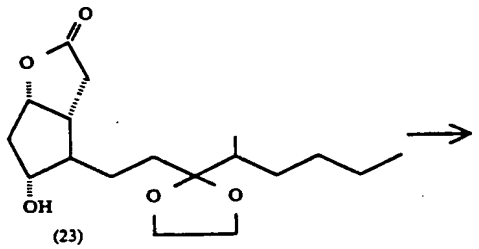

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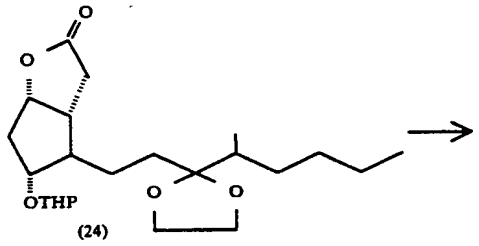

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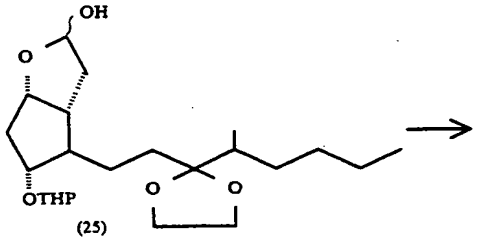

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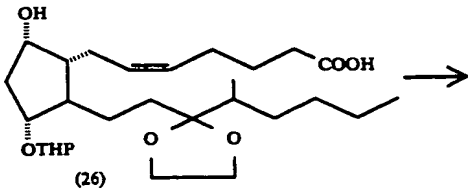

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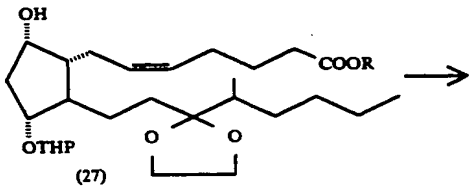

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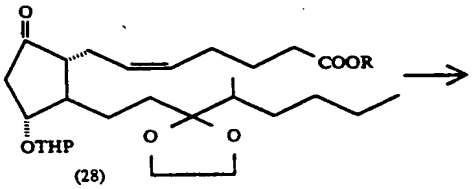

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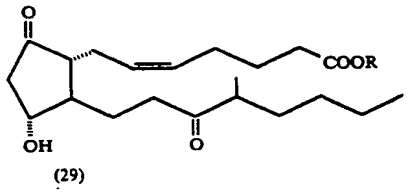

(29)

R: Et or Me

Chart IV

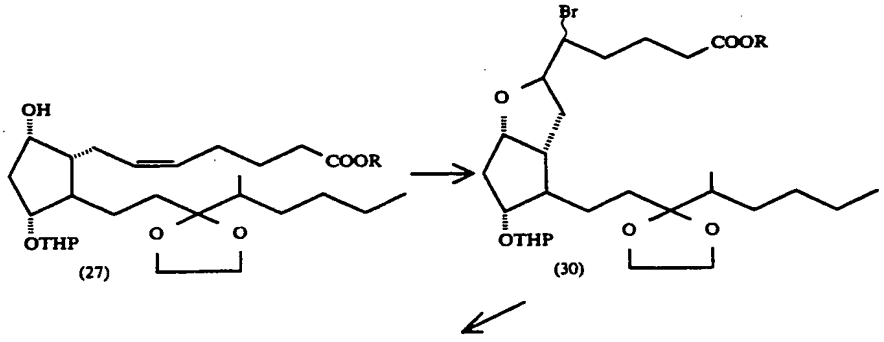

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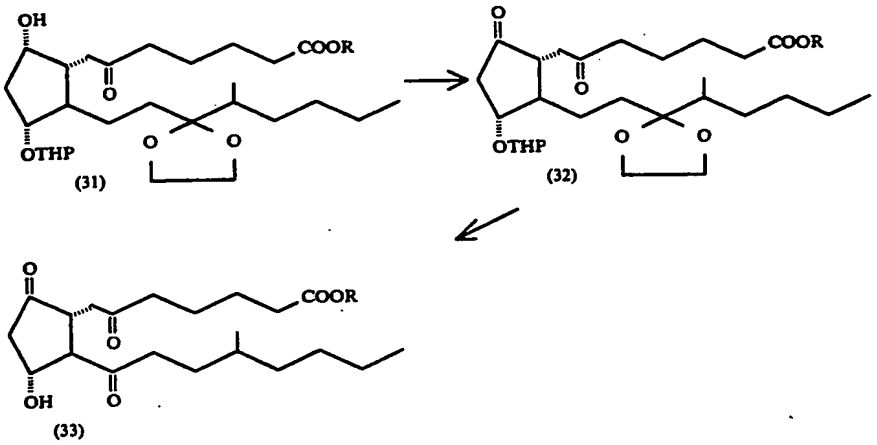
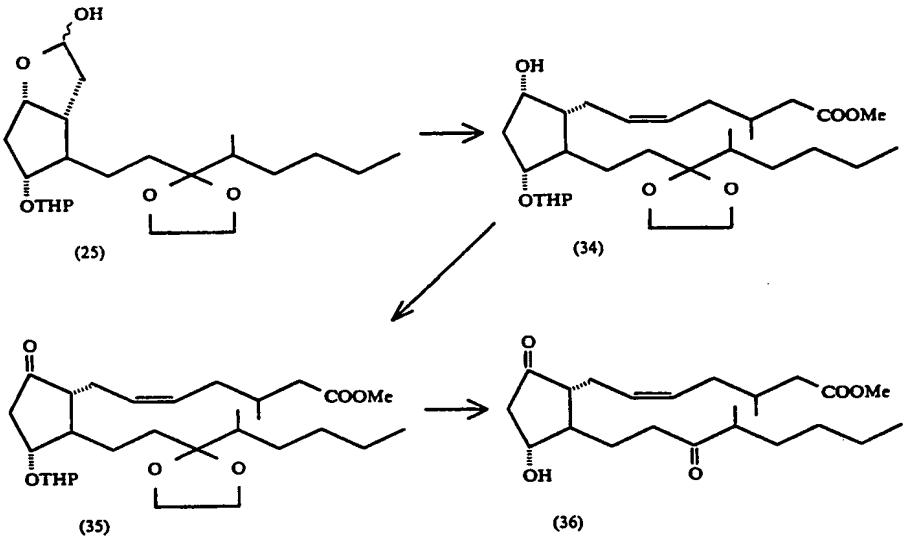
Chart IV



R: Et or Me

Chart V



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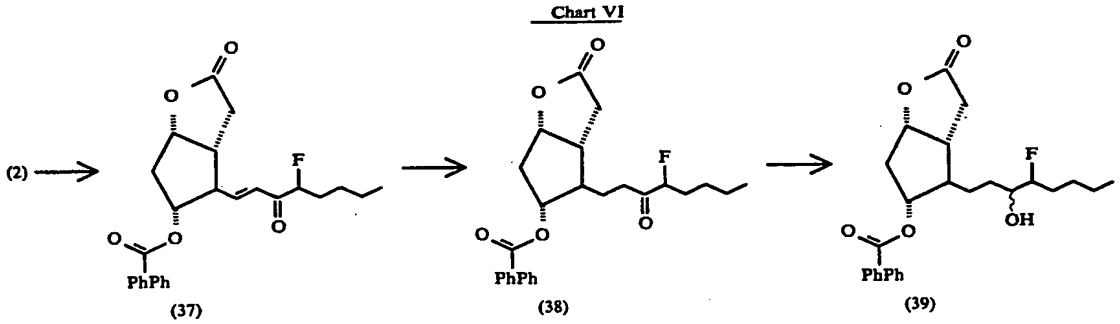

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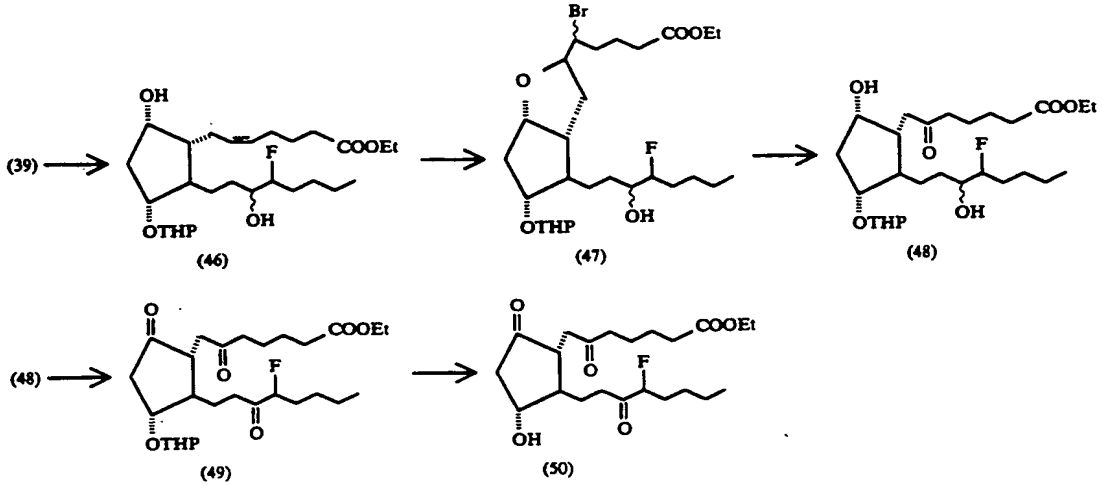

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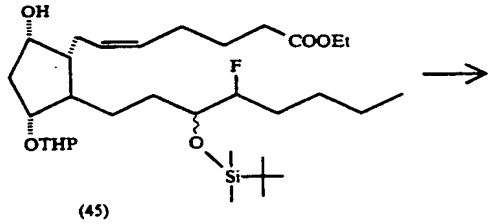

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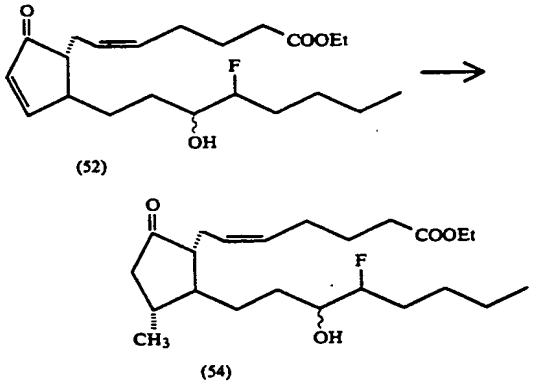

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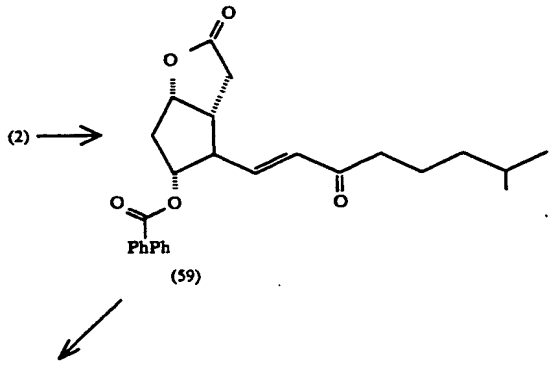

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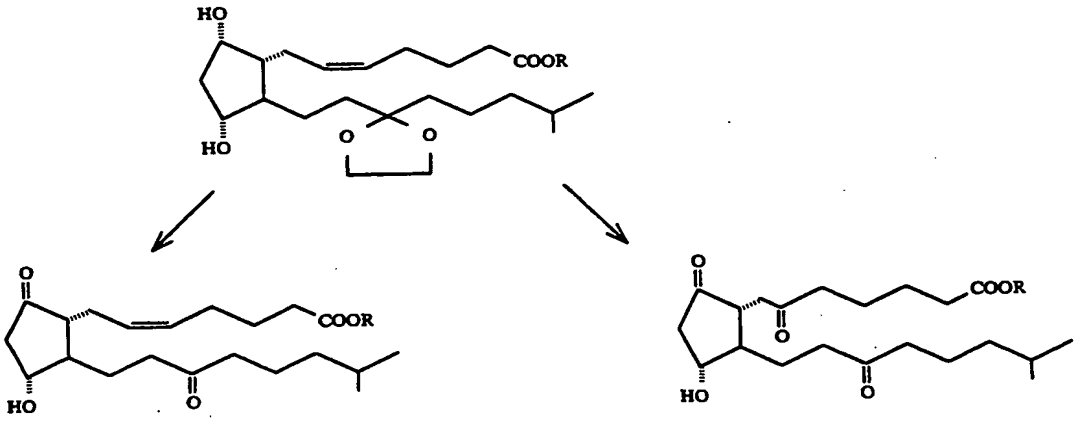
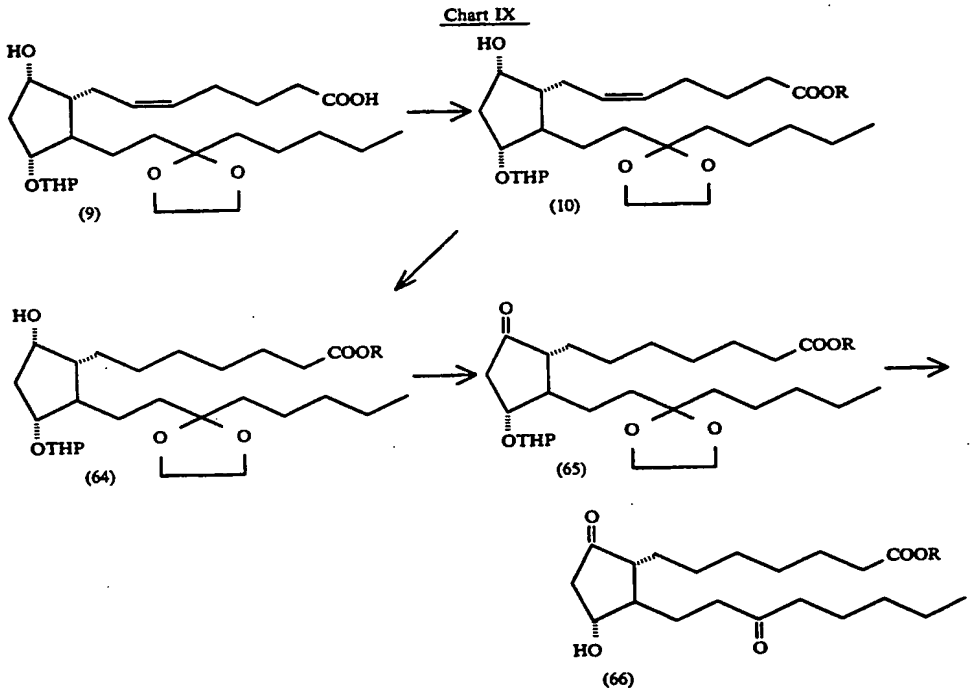


R: Et (60)
Me (61)

R: Et or Me

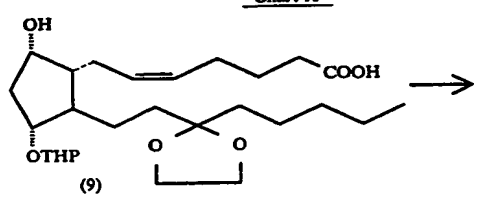
R: Et (62)
Me (63)

Chart IX



R: Et or Me

Chart X



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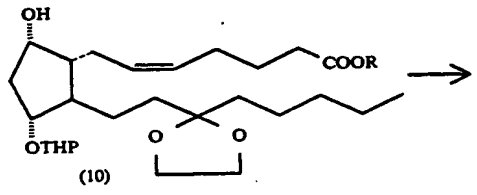

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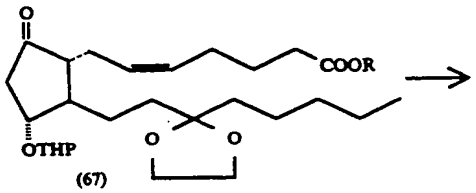
Chart X



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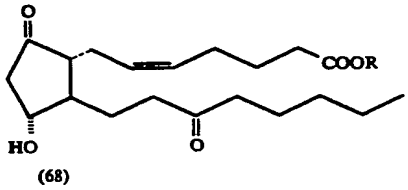

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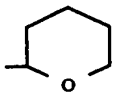
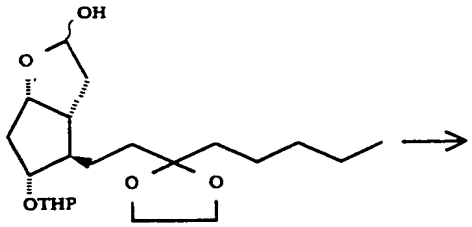
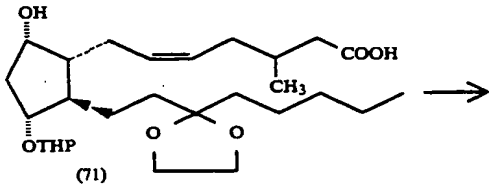


R = Et, Me, n-Pro, iso-Pro
iso-Pro, n-Bu,
Cyclopentyl, Benzyl

Chart XI





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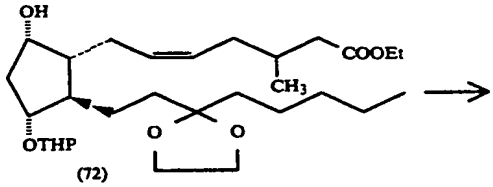

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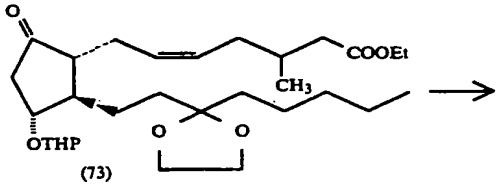

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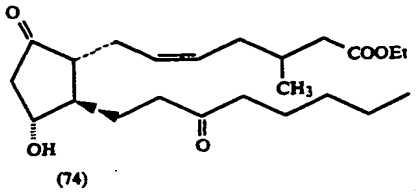

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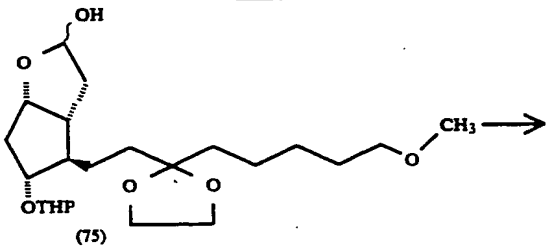

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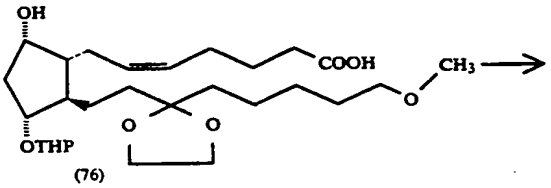

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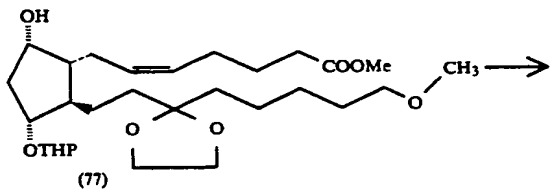

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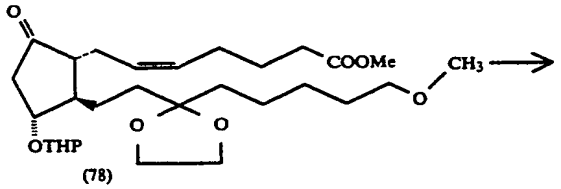

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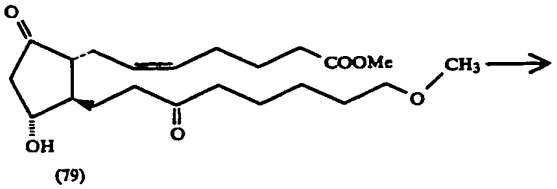

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Chart XIII

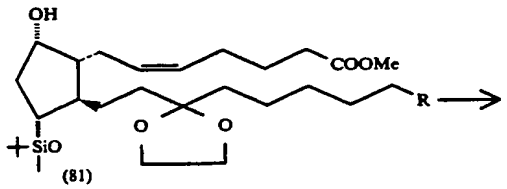

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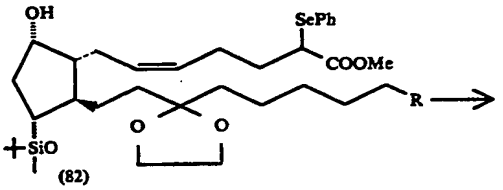
Chart XIII



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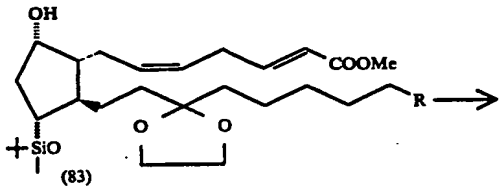

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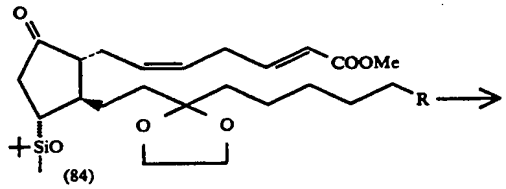

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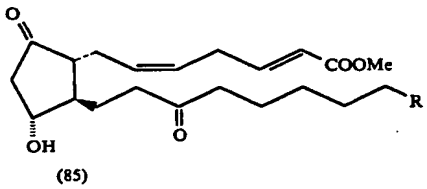

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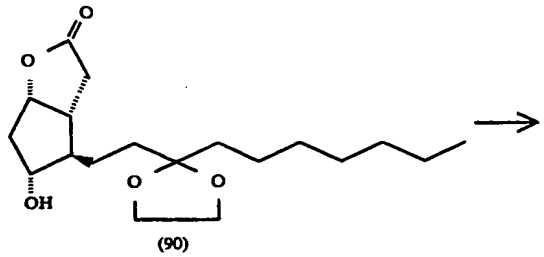

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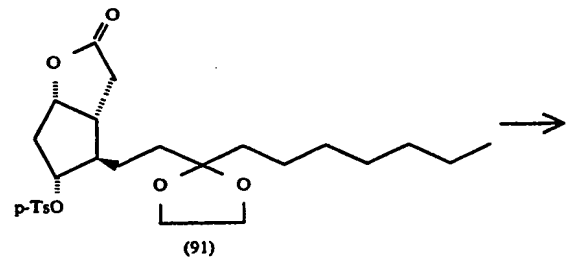

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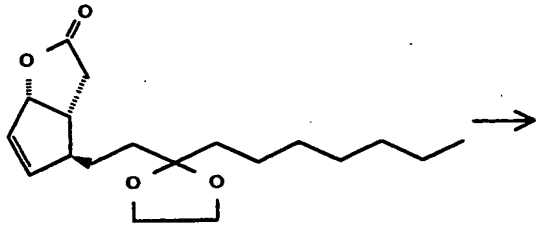
Chart XIV



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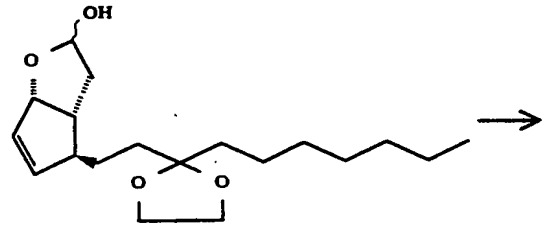

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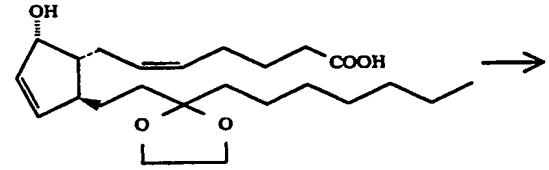

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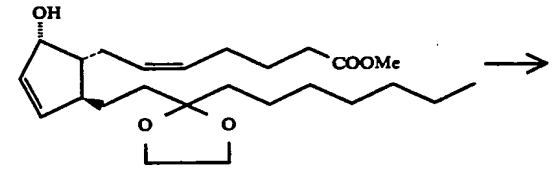

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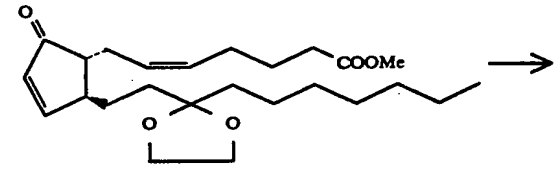

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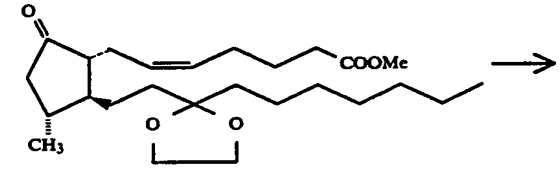

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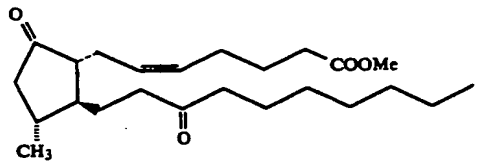

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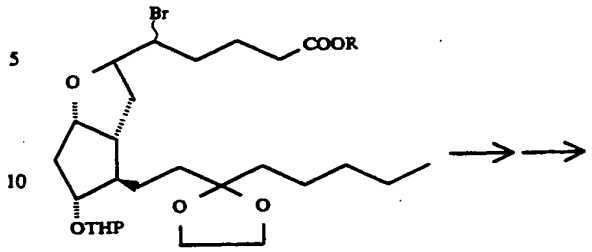

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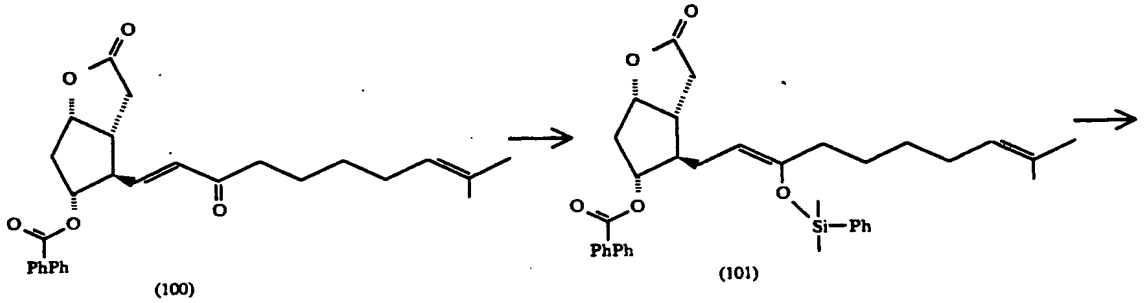

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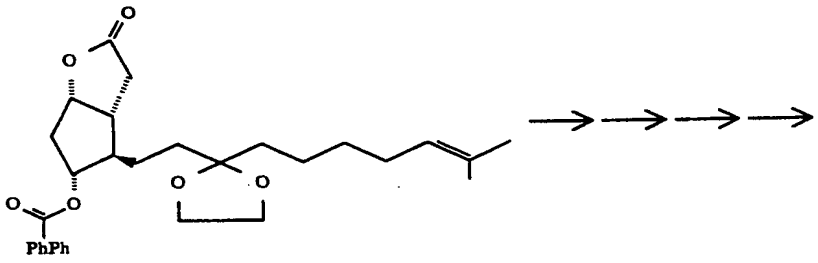
(101)



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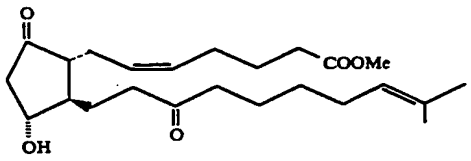

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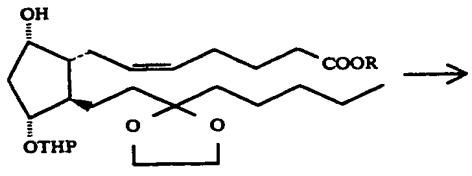
Chart XVI



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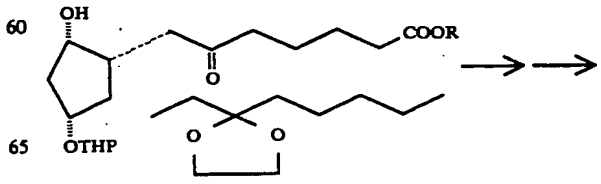

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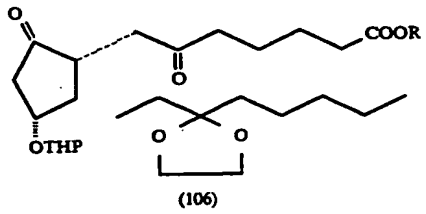

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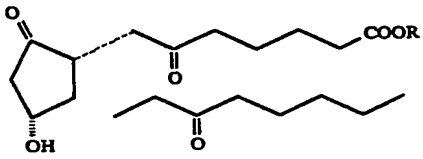

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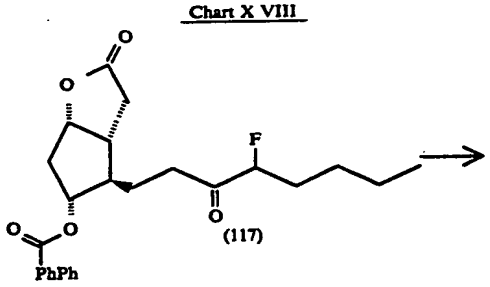

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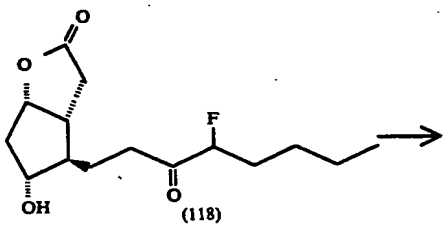

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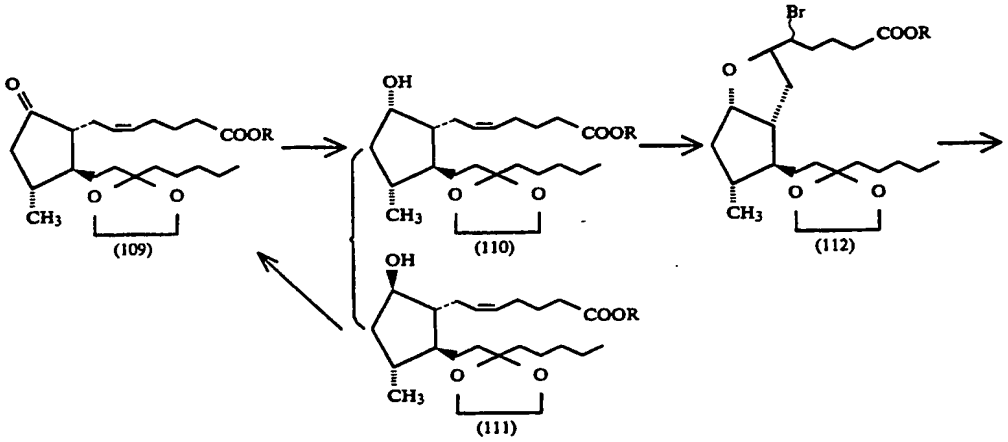

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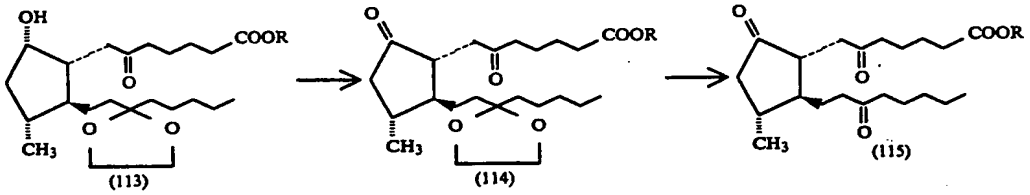

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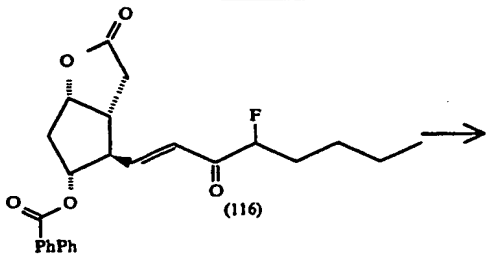
Chart X VIII



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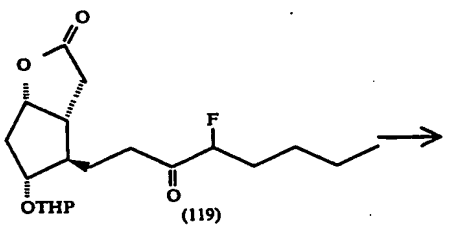

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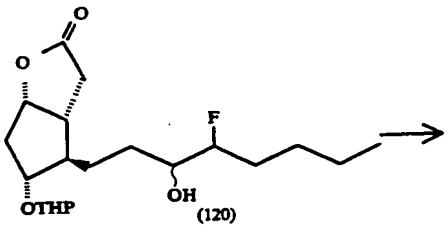

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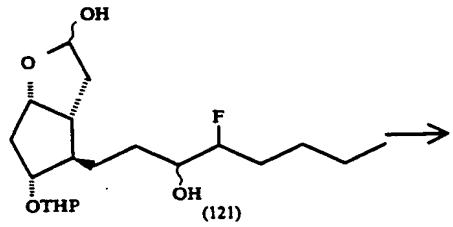

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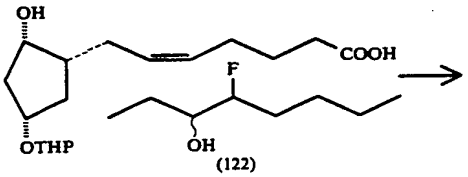

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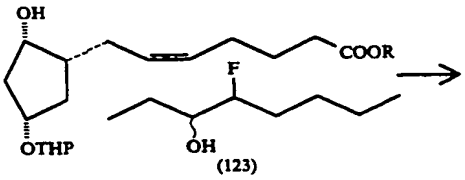
Chart X VIII



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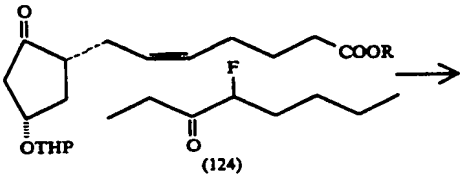

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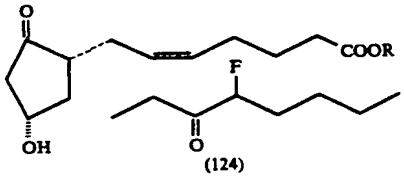

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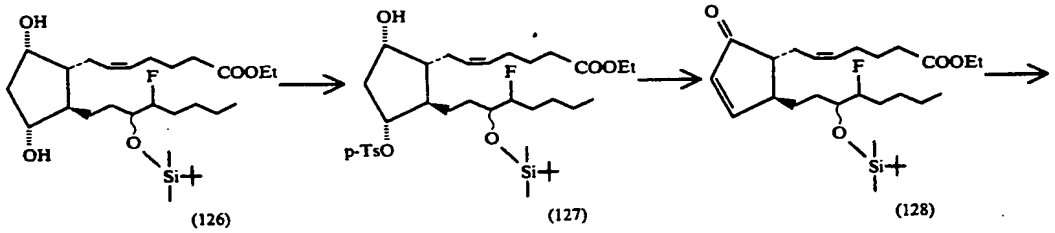
Chart X IX



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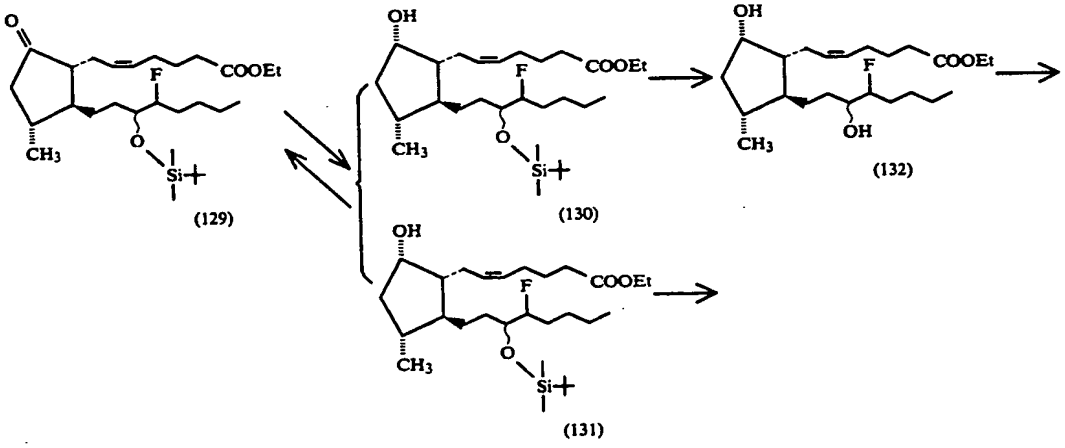

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Chart X IX

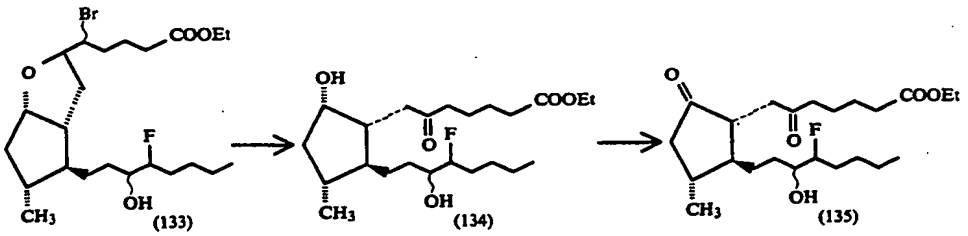
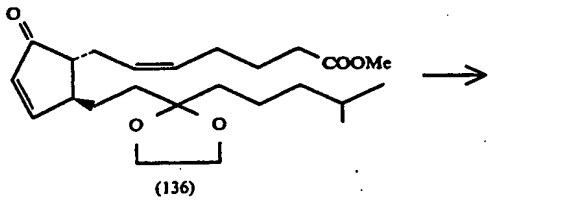
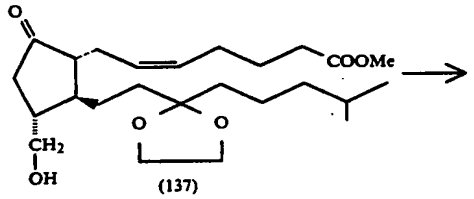


Chart XX





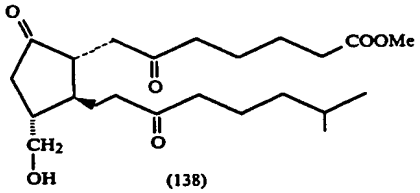
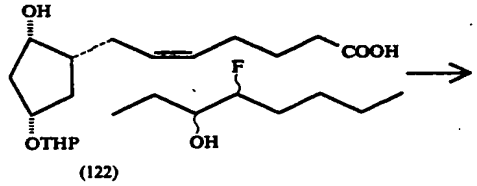
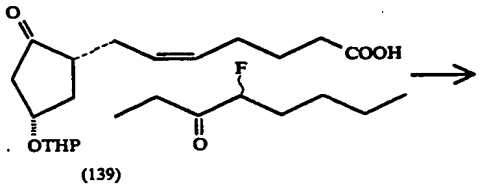
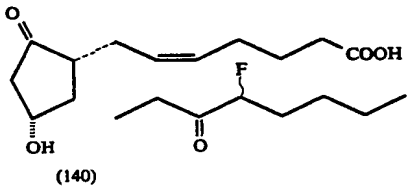


Chart XXI







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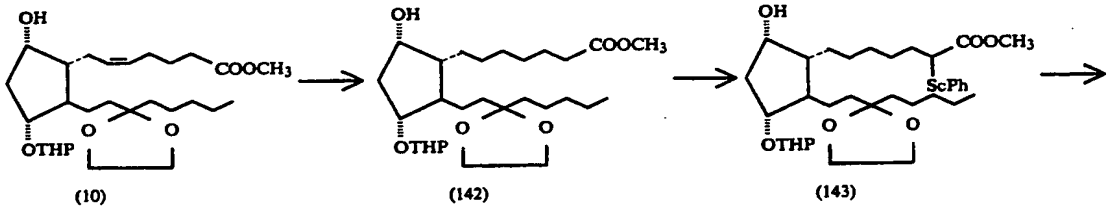

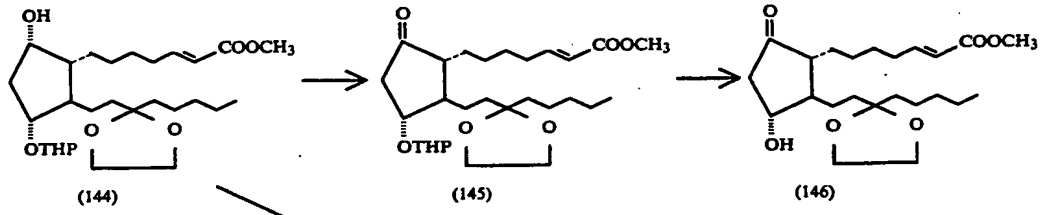

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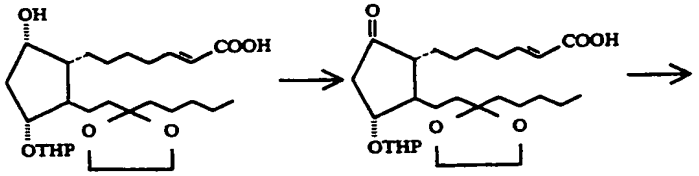
Chart XXII



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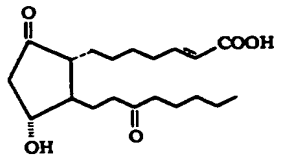
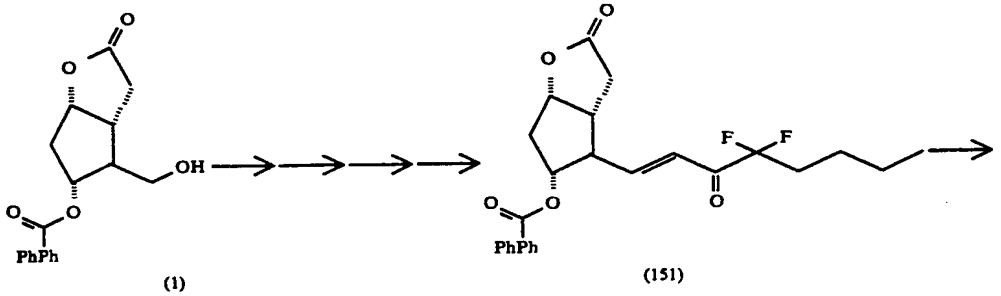


(149)

Chart XXIII



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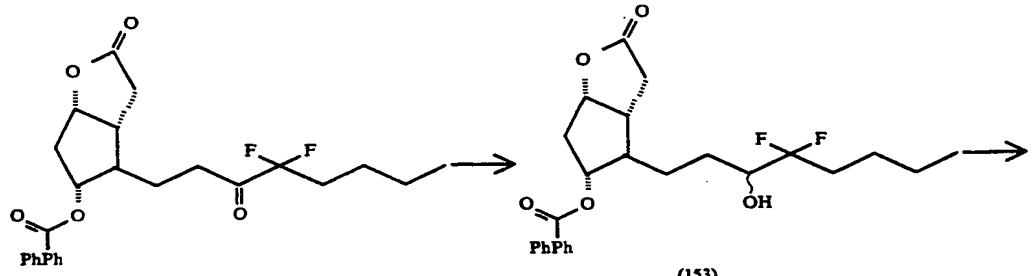

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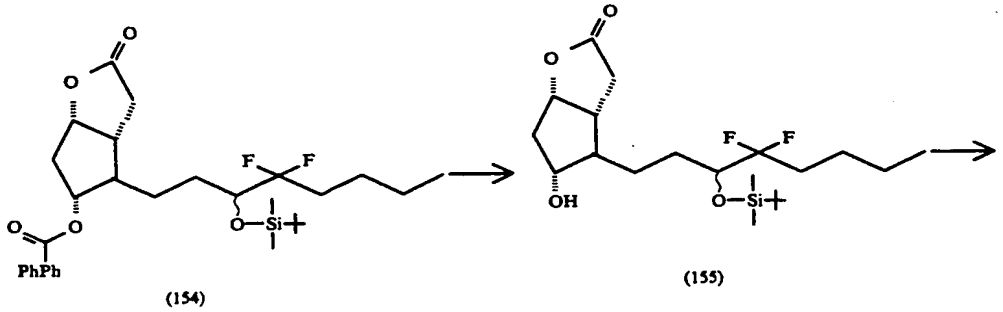

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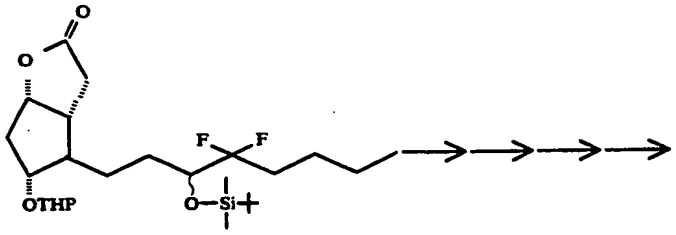
Chart XXIII



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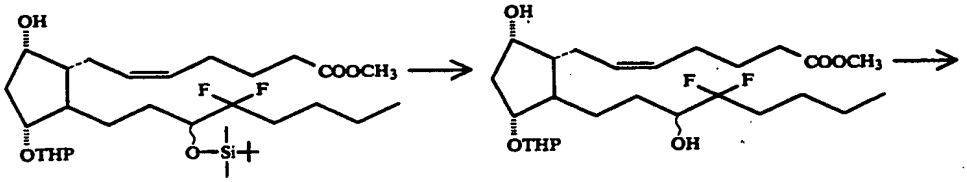

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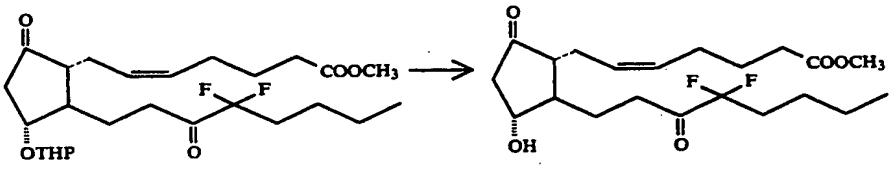

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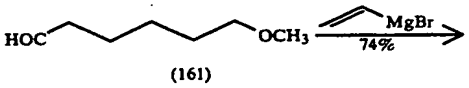

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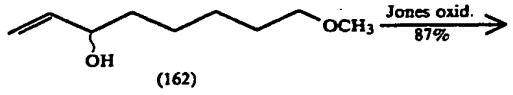

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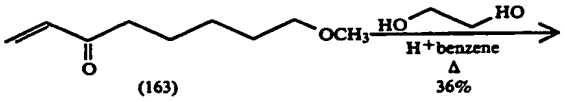

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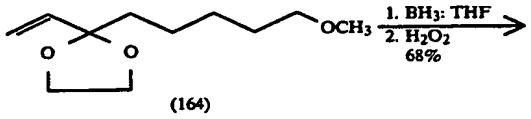

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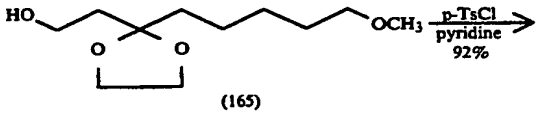

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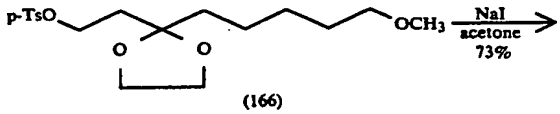

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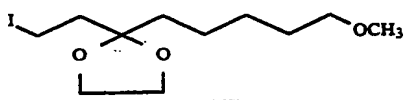
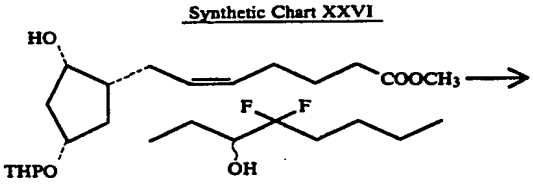
Chart XXIV



(167)

Synthetic Chart XXVI



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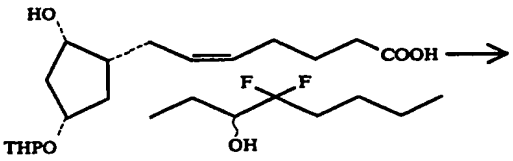

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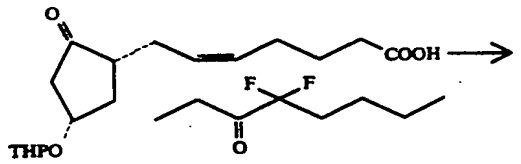
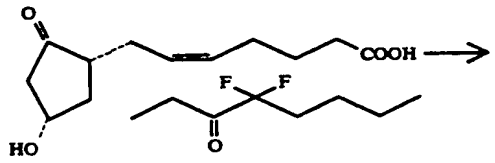
Synthetic Chart XXVI

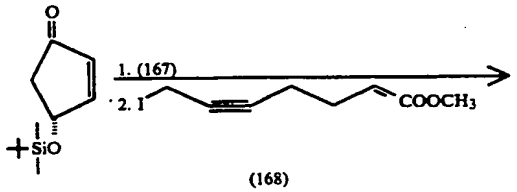


(173)



(174)

Chart XXV



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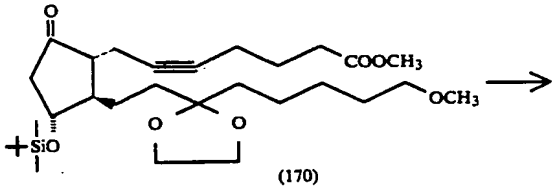

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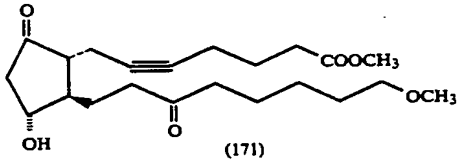
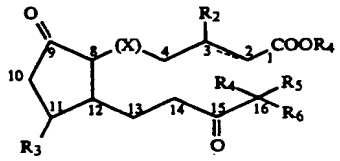


(171)

What is claimed is:

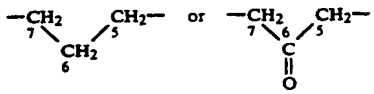
1. Prostaglandins E represented by a general formula:



(I)

in which

X represents:



R_1 represents: a hydrogen atom, a physiologically acceptable sat residue, or an ester residue selected from the group consisting of alkyl, benzyl, hydroxyalkyl, alkoxyalkyl, alkylsilyl and tetrahydropyranyl group;

R_2 represents: a hydrogen atom or a methyl group;

R_3 represents: a hydroxyl or hydroxymethyl group;

R_4 and R_5 each represents: a hydrogen atom, a methyl group or a halogen atom provided that at least one of R4 and R5 is a halogen atom; and

R_6 represents: a C_1–C_9 alkyl group which may have a branch or a double bond, or a C_1–C_9 alkyl group having an alkoxy substituent group, the C_2–C_3 bond being a single or double bond.

2. Prostaglandins E as described in claim 1, wherein R_4 and R_5 are halogen atoms.

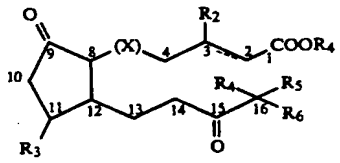
3. Prostaglandins E as described in claim 1, wherein R_4 and/or R_5 is a fluorine atom.

4. Prostaglandins E as described in claim 1, wherein R_4 or R_5 is a methyl group.

5. Prostaglandins E as described in claim 1, which is 13,14-dihydro-15-keto-PGE having one or more fluorine atom(s) on 16-position or alkyl ester thereof.

6. Prostaglandins E as described in claim 1, being 13,14-dihydro-6,15-diketo-16R,S-fluoro-PGE_1 or alkyl ester thereof.

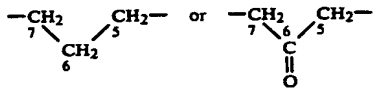
7. An anti-ulcer composition comprising an anti-ulcer effective amount of a prostaglandin E expressed by a general formula:



(I)

in which

X represents:



R_1 represents: a hydrogen atom, a physiologically acceptable sat residue, or an ester residue selected from the group consisting of alkyl, benzyl, hydroxyalkyl, alkoxyalkyl, alkylsilyl and tetrahydropyranyl group;

R_2 represents: a hydrogen atom or a methyl group;

R_3 represents: a hydroxyl or hydroxymethyl group;

R_4 and R_5 each represents: a hydrogen atom, a methyl group or a halogen atom provided that at least one of R_4 and R_5 is a halogen atom; and

R_6 represents: a C_1–C_9 alkyl group which may have a branch or a double bond, or a C_1–C_9 alkyl group having an alkoxy substituent group, the C_2–C_3 bond being a single or double bond.

8. An anti-ulcer composition as in claim 7, wherein R_4 and R_5 are halogen atoms.

9. An anti-ulcer composition as in claim 7, wherein R_4 and/or R_5 is a fluorine atom.

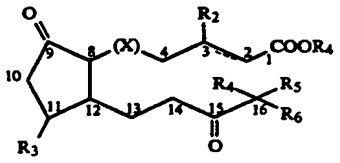
10. An anti-ulcer composition as in claim 7, wherein R_4 or R_5 is a methyl group.

11. An anti-ulcer composition as in claim 7, wherein the prostaglandin E is 13,14-dihydro-15-PGE having

one or more fluorine atom(s) on 16-position or alkyl ester thereof.

12. An anti-ulcer composition as in claim 7, wherein the prostaglandin E is 13,14-dihydro-6,15-diketo-16R,S-fluoro-PGE$_1$ or alkyl ester thereof.

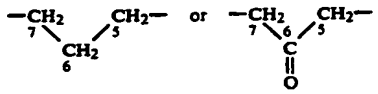
13. A treatment of ulcer by administering an anti-ulcer treating effective amount of prostaglandin E to a patient, wherein the prostaglandin E is represented by a formula:



(I)

in which

X represents:



R_1 represents: a hydrogen atom, a physiologically acceptable salt residue, or an ester residue selected from the group consisting of alkyl, benzyl, hydroxyalkyl, alkoxyalkyl, alkylsilyl and tetrahydropyranyl group;

R_2 represents: a hydrogen atom or a methyl group;

R_3 represents: a hydroxyl or hydroxymethyl group;

R_4 and R_5 each represents: a hydrogen atom, a methyl group or a halogen atom provided that at least one of R_4 and R_5 is a halogen atom; and

R_6 represents: a C_1–C_9 alkyl group which may have a branch or a double bond, or a C_1–C_9 alkyl group having an alkoxy substituent group, the C_2–C_3 bond being a single or double bond.

* * * * *

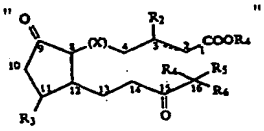
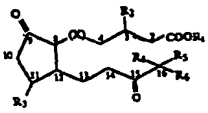
EXHIBIT 5

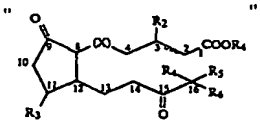
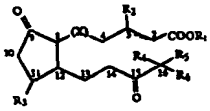
UNITED STATES PATENT AND TRADEMARK OFFICE

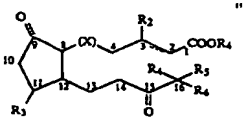
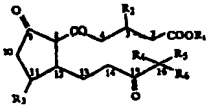
CERTIFICATE OF CORRECTION

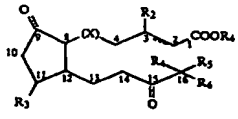
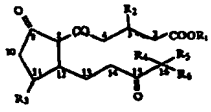
PATENT NO. : 5,284,858
DATED : February 8, 1994
INVENTOR(S) : Ryuzo Ueno et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 3,
Line 1, delete "  " and insert --  --.

Column 77,
Line 50, delete "  " and insert --  --.

Column 78,
Line 30, delete "  " and insert --  --.

Column 79,
Line 11, delete "  " and insert --  --.

Signed and Sealed this

Seventh Day of September, 2004

JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT 6

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer Num: 204

COMPUTER PACKAGES, INC.
414 HUNGERFORD DRIVE
ROCKVILLE MD 20850

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,284,858	**$1,020.00**	**$0.00**	**07/925,220**	**02/08/94**	**08/06/92**	**04**	**NO**	**PAID**	**Q-29894**

Direct any questions about this notice to:
Mail Stop M Correspondence
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

RAMPS 03/07/2006 10:05:09 AM EST

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer Num: 204

COMPUTER PACKAGES, INC.
414 HUNGERFORD DRIVE
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MAINTENANCE FEE STATEMENT

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If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,284,858	**$3,800.00**	**$0.00**	**07/925,220**	**02/08/94**	**08/06/92**	**12**	**NO**	**PAID**	**Q-29894**

Direct any questions about this notice to:
Mail Stop M Correspondence
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

EXHIBIT 7

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21908

NAME OF APPLICANT / NDA HOLDER
Sachiko Kuno, PhD
CEO, Sucampo Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ETREVA

ACTIVE INGREDIENT(S)	STRENGTH(S)
Lubiprostone	24 mcg

DOSAGE FORM
Liquid Gelatin Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5284858	2/8/1994	2/8/2011

d. Name of Patent Owner
Sucampo AG

Address *(of Patent Owner)*
Graben 5,

City/State
Zug, Switzerland

ZIP Code	FAX Number *(if available)*
CH-6300	41-1-252-9804

Telephone Number	E-Mail Address *(if available)*
41-1-262-4678	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*
4733 Bethesda Ave, Ste 450

City/State
Bethesda, MD

ZIP Code	FAX Number *(if available)*
20814	301.961.3440

Telephone Number	E-Mail Address *(if available)*
301.961.3400	s kuno@sucampo.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

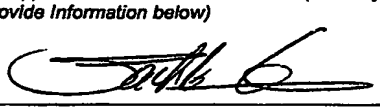
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	03/31/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Sachiko Kuno, PhD, CEO, Sucampo Pharmaceuticals, Inc.	
Address 4733 Bethesda Ave, Ste 450	City/State Bethesda, MD
ZIP Code 20814	Telephone Number 301.961.3400
FAX Number *(if available)* 301.961.3440	E-Mail Address *(if available)* s.kuno@sucampo.com

EXHIBIT 8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of:

Ryuzo UENO, et al. Docket No: 004406

U.S. Patent No.: 5,284,858

Issued: February 8, 1994

For: PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME

POWER OF ATTORNEY AND APPOINTMENT OF AGENT

PURSUANT TO 37 C.F.R. § 1.730

MAIL STOP: Patent Term Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant, Sucampo AG, a corporation organized and existing under the laws of Switzerland, and having a principal place of business at Graben 5, CH-6300, Zug, Switzerland, represents that it is the Assignee of the entire right, title and interest in and to United States Letters Patent No. 5,284,858, granted to Ryuzo Ueno, Ryuji Ueno, Ichie Kato and Tomio Oda on February 8, 1994, for PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME by virtue of an Assignment from the inventors in favor of Kabushiki Kaisha Ueno Seiyaku Oyo Kenkyujo, recorded in the U.S. Patent and Trademark Office on October 18, 1989, at Reel 5167, Frame 423-424, and subsequently, an Assignment from Kabushiki Kaisha Ueno Seiyaku Oyo Kenkyujo to Sucampo AG, recorded in the U.S. Patent and Trademark Office on June 13, 2001, at Reel 011887, Frame 0481.

POWER OF ATTORNEY AND APPOINTMENT OF AGENT PURSUANT TO 37 C.F.R. § 1.730
U.S. Patent No.: 5,284,858

Attorney Docket No. 004406

Applicant, Sucampo AG, as the owner of record of the above-identified United States Letters Patent, hereby appoints the practitioners at CUSTOMER NO. 23373 (SUGHRUE MION, PLLC) as its attorneys to conduct all business before the United States Patent and Trademark Office relative to an application for patent term extension pursuant to 35 U.S.C. § 156 for the above-identified United States Letters Patent.

It is requested that all correspondence relative to the same be directed to Bruce E. Kramer, SUGHRUE MION, PLLC, 2100 Pennsylvania Ave., N.W., Washington, DC 20037-3213, whose telephone number is (202) 293-7060, and any telephonic communications relative to the same are also to be conducted with one of the attorneys listed under CUSTOMER NO. 23373 at the telephone number listed immediately above.

The undersigned (whose title is supplied below) is empowered to sign this Power of Attorney and Appointment of Agent on behalf of the Assignee.

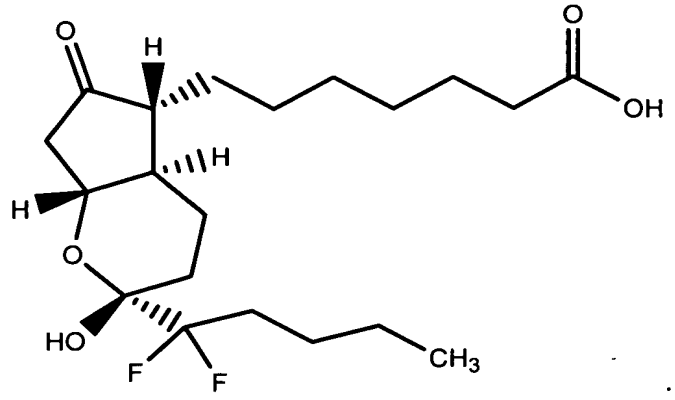
Date: March 22, 2006

Sucampo AG

By: Misako Nakata

Name: Misako Nakata
Title: Authorized Signing Officer

EXHIBIT 9



(2) **A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED.**

The approved product, AMITIZA™, was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505 (21 U.S.C. § 355).

(3) **AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED.**

The approved product, AMITIZA™, received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on January 31, 2006. A copy of the permission letter including Package Insert is attached hereto as Exhibit 3.

(4) **IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FDC ACT, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN**

ACT, OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED.

The active ingredient in AMITIZA™ is lubiprostone. Lubiprostone has not been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxic Act prior to the approval of NDA 21-908 by the Food and Drug Administration on January 31, 2006.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO 37 C.F.R. § 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED.

This application for Extension of Patent Term Under 35 U.S.C. § 156 is being submitted within the permitted sixty day period pursuant to 37 C.F.R. § 1.720(f). Said period will expire on April 1, 2006.

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION.

The complete identification of the Patent for which extension is being sought is as follows:

Inventors: Ryuzo Ueno, Ryuji Ueno, Ichie Kato, and Tomio Oda

U.S. Patent No.: 5,284,858

Issue Date: February 8, 1994

Expiration Date: February 8, 2011 (17 years after the issue date)

(7) **A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS.**

A complete copy of U.S. Patent No. 5,284,858 is attached hereto as Exhibit 4.

(8) **A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR REEXAMINATION CERTIFICATE ISSUED IN THE PATENT.**

No Disclaimer or Reexamination Certificate has been issued with respect to U.S. Patent No. 5,284,858.

A Certificate of Correction was requested and issued on September 7, 2004 with respect to U.S. Patent No. 5,284,858. A copy of the Certificate of Correction is attached hereto as Exhibit 5.

Maintenance fee payments have also been made for U.S. Patent No. 5,284,858; attached hereto as Exhibit 6 are papers relating to the maintenance fee payments, as follows:

(a) A Maintenance Fee Statement showing the status of the first maintenance fee payment required at 3 ½ years as "paid,"

(b) A Maintenance Fee Statement showing the status of the first maintenance fee payment required at 7 ½ years as "paid," and

(c) A Maintenance Fee Statement showing the status of the first maintenance fee payment required at 11 ½ years as "paid."

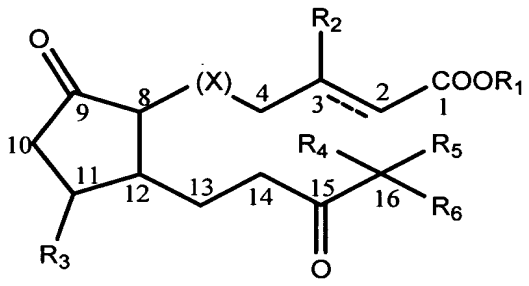
(9) **A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT**

CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE APPROVED PRODUCT.

U.S. Patent No. 5,284,858 claims the approved product, and also claims an anti-ulcer composition comprising the approved product and a method of using the approved product.

Claim 1

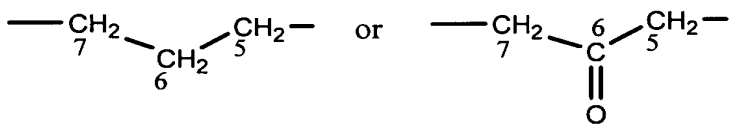
Prostaglandins E represented by a general formula:



(I)

in which

X represents:



R_1 represents: a hydrogen atom, a physiologically acceptable sat[1] residue, or an ester residue selected from the group consisting of alkyl, benzyl, hydroxyalkyl, alkoxyalkyl, alkylsilyl and tetrahydropyranyl group;

R_2 represents: a hydrogen atom or a methyl group;

R_3 represents: a hydroxyl or hydroxymethyl group;

---

[1] There is a typographical error in which "sat" should be "salt."

R_4 and R_5 each represents: a hydrogen atom, a methyl group or a halogen atom provided that at least one of R_4 and R_5 is a halogen atom; and

R_6 represents: a C_1-C_9 alkyl group which may have a branch or a double bond, or a C_1-C_9 alkyl group having an alkoxy substituent group, the C_2-C_3 bond being a single or double bond.

Claim 2

Prostaglandins E as described in claim 1, wherein R_4 and R_5 are halogen atoms.

Claim 3

Prostaglandins E as described in claim 1, wherein R_4 and/or R_5 is a fluorine atom.

Claim 4

Prostaglandins E as described in claim 1, wherein R_4 or R_5 is a methyl group.

Claim 5

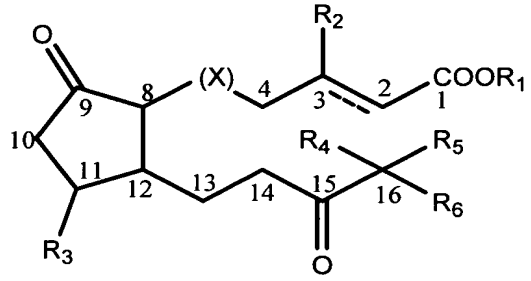
Prostaglandins E as described in claim 1, which is 13,14-dihydro-15-keto-PGE having one or more fluorine atom(s) on 16-position or alkyl ester thereof.

Claim 6

Prostaglandins E as described in claim 1, being 13,14-dihydro-6,15-diketo-16R,S-fluoro-PGE_1 or alkyl ester thereof.

Claim 7

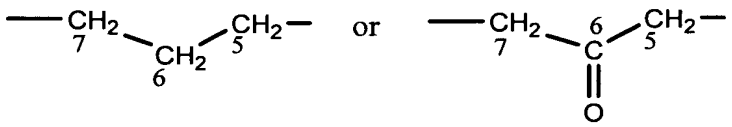
An anti-ulcer composition comprising an anti-ulcer effective amount of a prostaglandin E expressed by a general formula:



(I)

in which

X represents:



R_1 represents: a hydrogen atom, a physiologically acceptable sat[2] residue, or an ester residue selected from the group consisting of alkyl, benzyl, hydroxyalkyl, alkoxyalkyl, alkylsilyl and tetrahydropyranyl group;

R_2 represents: a hydrogen atom or a methyl group;

---

[2] There is a typographical error in which "sat" should be "salt."

R_3 represents: a hydroxyl or hydroxymethyl group;

R_4 and R_5 each represents: a hydrogen atom, a methyl group or a halogen atom provided that at least one of R_4 and R_5 is a halogen atom; and

R_6 represents: a C_1-C_9 alkyl group which may have a branch or a double bond, or a C_1-C_9 alkyl group having an alkoxy substituent group, the C_2-C_3 bond being a single or double bond.

Claim 8

An anti-ulcer composition as in claim 7, wherein R_4 and R_5 are halogen atoms.

Claim 9

An anti-ulcer composition as in claim 7, wherein R_4 and/or R_5 is a fluorine atom.

Claim 10

An anti-ulcer composition as in claim 7, wherein R_4 or R_5 is a methyl group.

Claim 11

An anti-ulcer composition as in claim 7, wherein the prostaglandin E is 13,14-dihydro-15-PGE[3] having one or more fluorine atom(s) on 16-position or alkyl ester thereof.

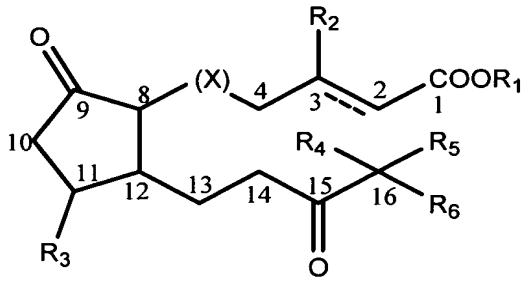
[3] "13,14-dihydro-15-PGE" should be "13,14-dihydro-15-keto-PGE." This is an obvious error in view of the formula (I) of claim 7, from which claim 11 depends.

Claim 12

An anti-ulcer composition as in claim 7, wherein the prostaglandin E is 13,14-dihydro-6,15-diketo-16R,S-fluoro-PGE_1 or alkyl ester thereof.

Claim 13

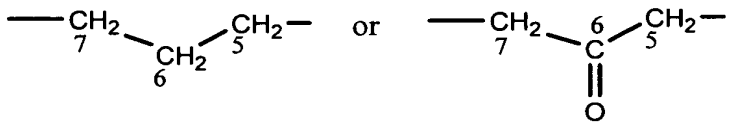
A treatment of ulcer by administering an anti-ulcer treating effective amount of prostaglandin E to a patient, wherein the prostaglandin E is represented by a formula:



(I)

in which

X represents:



R_1 represents: a hydrogen atom, a physiologically acceptable salt residue, or an ester residue selected from the group consisting of alkyl, benzyl, hydroxyalkyl, alkoxyalkyl, alkylsilyl and tetrahydropyranyl group;

R_2 represents: a hydrogen atom or a methyl group;

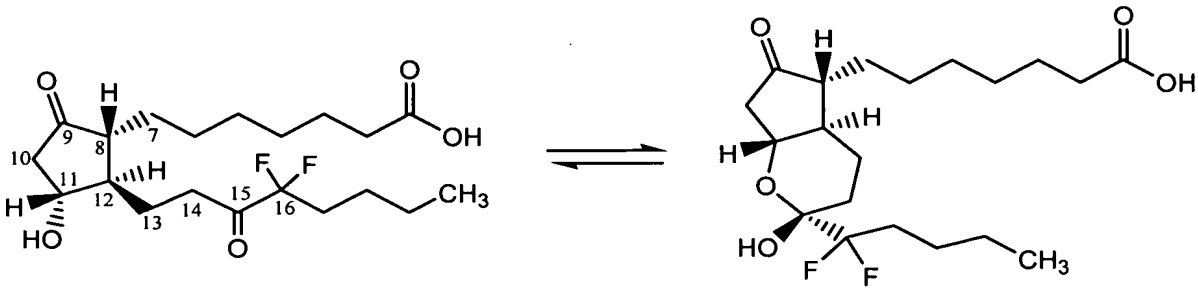
R_3 represents: a hydroxyl or hydroxymethyl group;

R_4 and R_5 each represents: a hydrogen atom, a methyl group or a halogen atom provided that at least one of R_4 and R_5 is a halogen atom; and

R_6 represents: a C_1-C_9 alkyl group which may have a branch or a double bond, or a C_1-C_9 alkyl group having an alkoxy substituent group, the C_2-C_3 bond being a single or double bond.

The applicable patent claims that read on lubiprostone are claims 1-3, 5, 7-9, 11 and 13.

Claim 1 reads on lubiprostone when X is $-CH_2CH_2CH_2-$, R^1 and R^2 are hydrogen atoms, R^3 is a hydroxyl group, R^4 and R^5 are fluorine atoms, R^6 is n-butyl group, the C_2-C_3 bond is a single bond in formula (I), and 8-, 11- and 12-positions have *R* configuration, and this compound is in the form of its tautomeric isomer, where the hydroxyl group at 11-position and the carbonyl group of 15-position combine to form a hemiacetal:



The Applicant notes that the specification defines that the prostaglandin Es of the present invention include isomers of the aforementioned compounds, that examples of these isomers include tautomeric isomers between the hydroxyl group at the 11-position and the carbonyl ground at the 15-position, i.e., a hemiacetal, and that such a tautomreic isomer is easily formed in

a compound having an electron attractive group such as a fluorine atom (see col. 4, lines 49-55). In view of this definition of the prostaglandin compound, the prostaglandin compound recited for the claimed invention includes its tautomer, such that the claimed invention includes within its scope, the tautomer of the prostaglandin compound in addition to the prostaglandin compound itself. The Applicant notes that he may be his own lexicographer by clearly setting forth a definition of a term. *In re Paulsen,* 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994).

Claim 2 reads on lubiprostone for the same reasons as claim 1, where R^4 and R^5 are fluorine atoms.

Claim 3 reads on lubiprostone for the same reasons as claim 2.

Claim 5 reads on lubiprostone for the same reasons as claim 1.

Claim 7 reads on lubiprostone for the same reasons as claim 1.

Claim 8 reads on lubiprostone for the same reasons as claim 2.

Claim 9 reads on lubiprostone for the same reasons as claim 2.

Claim 11 reads on lubiprostone for the same reasons as claim 1.

Claim 13 reads on lubiprostone for the same reasons as claim 1.

(10) A STATEMENT, BEGINNING ON A NEW PAGE, OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. § 156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD.

The relevant dates and information pursuant to 35 U.S.C. 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i)(A) Investigational New Drug Application (IND 59,623) for an oral formulation for the treatment of chronic idiopathic constipation in the adult population was filed with the Food and Drug Administration ("FDA") on December 29, 1999, and became effective on January 29, 2000;

(i)(B) New Drug Application (NDA 21-908) for use of AMITIZA™ as an oral formulation for the treatment of chronic idiopathic constipation in the adult population was submitted to the FDA on March 31, 2005; and

(i)(C) New Drug Application (NDA 21-908) for use of AMITIZA™ as an oral formulation for the treatment of chronic idiopathic constipation in the adult population was approved by the FDA on January 31, 2006. A copy of Patent Information submitted with the filing of an NDA is attached hereto as Exhibit 7.

(11) A BRIEF DESCRIPTION, BEGINNING ON A NEW PAGE, OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES.

DATE TO/FROM FDA	DESCRIPTION
December 29, 1999	Initial IND Application (IND 59,623 for the oral formulation for treatment of chronic idiopathic constipation in the adult population)
January 6, 2000	Receipt of acknowledgement from the FDA
February 23, 2000	Submission of Protocol Amendment: Change in Protocol, New Investigator
March 10, 2000	Receipt of Response to IND Submission
March 10, 2000	Submission of Information Amendment, General Correspondence (Clinical Site Addition, Laboratory Site Addition)
March 28, 2000	Response to FDA RFI (Clinical and CMC Issues)
April 19, 2000	Response to FDA RFI (Efficacy Measures)
April 28, 2000	Submission of Protocol Amendment: Change in Protocol (Primary Endpoint; BMs)
April 28, 2000	Response to FDA RFI
April 28, 2000	Submission of Information Amendment: Chemistry/Microbiology (Stability Data)
September 29, 2000	Meeting Request (Type C (December))
October 17, 2000	Receipt of Denial of Toxicology Meeting Request
November 3, 2000	Submission of Protocol Amendment: New Protocol (PK Study), New Investigator
November 3, 2000	Submission of Information Amendment: Chemistry/Microbiology
December 8, 2000	Receipt of Response to Phase 1 Protocol Amendment
December 14, 2000	Submission of Carcinogenicity Waiver (Long-term Rodent Studies)
December 22, 2000	Submission of Protocol Amendment: Change in Protocol (PK Study)
December 22, 2000	Response to FDA RFI (Formulation Clarification)
January 17, 2001	Request to Submit Type B Meeting
January 24, 2001	Receipt of Confirmation of EOP2 Meeting
March 2, 2001	Submission of Annual Report (1st Annual Report)
March 9, 2001	General Correspondences with the FDA (End of Phase 2 (EOP2) Briefing Package)
April 17, 2001	Response to FDA RFI (EOP2 Meeting Minutes)
April 18, 2001	Request for Type B Meeting (CMC Issues)
April 30, 2001	Receipt of Denial of Request for Waiver

May 7, 2001	Receipt of Confirmation of EOP2 Meeting
May 14, 2001	Receipt of Official Minutes of EOP2 Meeting
May 16, 2001	General Correspondences with the FDA (Clarification of Meeting Minutes)
May 21, 2001	Response to FDA RFI
May 21, 2001	Submission of CMC Meeting Package (Type B CMC Meeting Package)
June 18, 2001	Receipt of Attendee List from EOP2 Meeting
June 28, 2001	General Correspondences with the FDA (Meeting Minutes for EOP3 CMC Meeting)
July 10, 2001	General Correspondence EOP2 CMC Meeting Minutes
July 20, 2001	Teleconference with the FDA
July 24, 2001	General Correspondences with the FDA (Minutes of Conference Call of Pediatrics Discussion, Teleconference Minutes (20 July 2001))
July 26, 2001	General Correspondence Teleconference Minutes
August 1, 2001	Receipt of Official Minutes of CMC EOP2 Minutes
August 17, 2001	Submission of Protocol Amendment: New Protocol (Protocol RTU/0211SC0131)
August 17, 2001	Submission of Information Amendment: Chemistry/Microbiology (Finished Product CMC), Pharmacology/Toxicology (Toxicology Reports)
September 11, 2001	General Correspondences with the FDA (Notification of Intended Carcinogenicity SPA)
October 26, 2001	Request for SPA (Carcinogenicity Protocol)
November 6, 2001	Receipt of Request for Assessment of Carc Study
November 8, 2001	Submission of Protocol Amendment: New Protocol (Protocol RTU/0211SC01S1), Change in Protocol (RTU/0211SC0131), New Investigator
November 8, 2001	Submission of Information Amendment: Chemistry/Microbiology (Dissolution Protocol), Pharmacology/Toxicology (Updated TK data)
November 16, 2001	Submission of Protocol Amendment: New Protocol (Protocol RTU/0211SC01S2)
December 4, 2001	Receipt of Response to Carc SPA Request
December 17, 2001	Response to CAC Report (Dosage Schedule)
December 21, 2001	Receipt of Response to Proposed Carc Study
January 4, 2002	Submission of Protocol Amendment: New Investigator (RTU/0211SC01S1; 01S2)
January 4, 2002	Submission of Information Amendment: Chemistry/Microbiology (Stability Protocol)
February 15, 2002	General Correspondence: Change of Name to SPI
February 26, 2002	Receipt of Receipt of Corporate Name Change

April 30, 2002	Submission of Information Amendment: Pharmacology/Toxicology (3 Reports)
April 30, 2002	Submission of Annual Report (2nd Annual Report)
July 5, 2002	General Correspondence: Protocol Deviation
July 9, 2002	Submission of Protocol Amendment: Change in Protocol (S1 (Amd 1.1.); S2 (Amd 1.1))
August 19, 2002	Submission of Protocol Amendment: New Investigation (SC01S1)
August 19, 2002	Submission of Information Amendment: Pharmacology/Toxicology (Repro Toxicology Protocol)
November 12, 2002	Submission of Protocol Amendment: New Protocol (Protocol RTU/0211SC0232)
January 8, 2003	Receipt of Response to Proposed Monkey Repro Study
January 13, 2003	General Correspondences with the FDA (Request for Clarification of Monkey Species)
February 4, 2003	Submission of Protocol Amendment: New Protocol (Protocol SPI/0211SC02S3)
February 4, 2003	Submission Information Amendment: Clinical (CTR99-004; CTR02-004; IB)
May 30, 2003	Submission of Protocol Amendment: New Investigator (0211SC02S3)
June 5, 2003	Submission of Annual Report (3rd Annual Report)
June 13, 2003	Submission of IND Safety Report: Initial Written Report (Congenital Clubfoot)
June 24, 2003	Submission of IND Safety Report: F/U to a Written Report (Updated CIOMS)
August 22, 2003	Submission of Protocol Amendment: New Investigator (SC0232 and SC02S3)
August 22, 2003	Submission of Information Amendment: Pharmacology/Toxicology, Clinical
August 22, 2003	Submission of Information Amendment: Chemistry/Microbiology (Chemistry Documents)
December 19, 2003	Submission of Information Amendment: Chemistry/Microbiology (^{3}H-0211)
January 16, 2004	Submission of Protocol Amendment: New Protocol (PK Study)
January 23, 2004	Submission of Protocol Amendment; New Investigator (SC0232 and SC02S3)
January 23, 2004	Submission of Information Amendment: Chemistry/Microbiology (^{3}H-0211 COAs), Pharmacology/Toxicology (Toxicology Studies)
February 4, 2004	Submission of Protocol Amendment: Change in Protocol (SPI/0211SA-0312 (Amd 1))
February 16, 2004	Submission of IND Safety Report: Initial Written Report (Diarrhea)
February 27, 2004	Pre-NDA Meeting Request (Type B Meeting (April))

March 19, 2004	Receipt of Denied Abortifacient Meeting Request
March 19, 2004	Receipt of Pre-NDA Meeting Confirmation
March 24, 2004	Teleconference with Dr. Justice
April 26, 2004	Pre-NDA Meeting Pkg (24-May-04 Meeting)
May 5, 2004	Submission of Annual Report: 4th Annual Report
May 14, 2004	General Correspondences with the FDA (Request for List of Attendees at Pre-NDA Meeting)
May 21, 2004	Receipt of Preliminary Pre-NDA Meeting Minutes
May 24, 2004	Receipt of Pre-meeting Response for Meeting
June 8, 2004	Submission of Protocol Amendment New Protocol (QTc Study)
June 8, 2004	Submission of Expedited Review
June 10, 2004	General Correspondence Pre-NDA Meeting Minutes
June 22, 2004	Receipt of Official Minutes of Pre-NDA Meeting; Enclosure
June 23, 2004	Submission of Proprietary Name Review
June 25, 2004	General Correspondences with the FDA (Corrections to FDA meeting Minutes)
July 8, 2004	Submission of Information Amendment: Chemistry/Microbiology (^{3}H-0211 COAs/Stability)
July 8, 2004	Submission of Investigator's Brochure Version 5
July 15, 2004	Receipt of Request for Information (QTc)
August 12, 2004	Submission of Protocol Amendment: Change in Protocol (SPI/0211SC0411 (Amd 1))
November 5, 2004	Response to FDA RFI QTc Study (7/15 Letter)
November 23, 2004	Submission of Protocol Amendment: New Investigator (Protocol SPI/0211SC0411)
February 1, 2005	Response to FDA RFI Biopharm and PK Data
July 8, 2005	Submission of Investigator's Brochure Version 6
December 21, 2005	Submission of Annual Report: 5th Annual Report

March 31, 2005	Original NDA submission
March 31, 2005	Submission of Request for deferral for pediatric studies
March 31, 2005	Submission of Field copy certification to Baltimore District Office
March 31, 2005	Submission of Field copy certification to CDER, FDA
April 11, 2005	Receipt of NDA receipt of acknowledgement (NDA 21-908 assigned)
May 16, 2005	Receipt of RFI: Historical control incidences of tumors (Carcinogenicity studies (rat/mouse))
June 9, 2005	Response to request for CMC information Required for FDA inspection
June 13, 2005	Response to RFI: Tumor data Covance studies

June 13, 2005	Receipt of Filing review (NDA is sufficient for review)
June 21, 2005	Receipt of RFI: Clinical documents Required for FDA inspection
June 23, 2005	Teleconference Clinical documents for inspection
July 1, 2005	Response to RFI: Clinical documents for 4 clinical sites
July 7, 2005	Receipt of Request for carcinogenicity data Biometrics format
July 12, 2005	Applicant Orientation Presentation slides PowerPoint slides (e-mail)
July 18, 2005	Receipt of Timeline for carcinogenicity date filing Mid-August acceptable date
July 21, 2005	Request for waiver and refund of PDUFA Fees (SPI is a small business)
July 27, 2005	4-month safety update report No new safety data
August 6, 2005	Request for Type A meeting Reproductive toxicology issues
August 11, 2005	Receipt of Request for size determination
August 17, 2005	Receipt of Proposed proprietary name
August 23, 2005	Receipt of Type A meeting confirmation (October 5, 2005, 12:00-1:00 P.M.)
September 9, 2005	Information package for Type A meeting 3 publications, PowerPoint
September 11, 2005	Receipt of Type A meeting details Format of presentation
September 13, 2005	Receipt of SBA/Formal size determination Small business confirmation
September 16, 2005	Submission of Carcinogenicity data Biometrics format
September 30, 2005	Submission of Packaging site; process parameter revised tox report 3-part submission
October 4, 2005	Receipt of Response to Type A meeting questions (3 questions)
October 14, 2005	Submission of Type A meeting presentation materials
October 31, 2005	Receipt of PDUFA fee waiver/refund Waiver/refund granted
November 2, 2005	Receipt of Type A meeting minutes "Review is ongoing"
November 10, 2005	Receipt of PREA discussion (Request for pediatric assessment)
November 16, 2005	Submission of 36-month stability data for capsules HDPE bottles and blister pack
November 22, 2005	Receipt of Rejection of proprietary name "Etreva"
December 7, 2005	Submission of Proposed proprietary name "Amitiza"
December 7, 2005	Submission of Revised 4-month safety update report (Dates specified)
December 9, 2005	Receipt of Discipline Response Letter (DMF deficiency)
December 21, 2005	Response to Discipline Response Letter (DMF deficiency resolved)
December 23, 2005	Receipt of RFI: Revision to Figure 1 labeling (Median SBM values requested)
January 3, 2006	Response to RFI: Figure 1 labeling (Median SBM values prepared)
January 12, 2006	Receipt of RFI: Revision to Figure 1 labeling (Interquartile ranges requested)
January 13, 2006	Receipt of 1st FDA revision to labeling text and packaging (Label negotiations)

January 18, 2006	Receipt of 2nd FDA revision to labeling text (Label negotiations)
January 19, 2006	Submission of 1st SPI revision to labeling text (Label negotiations)
January 22, 2006	Submission of 1st SPI revision to packaging (Label negotiations)
January 23, 2006	Submission of 1st SPI revision to packaging follow-up (Label negotiations)
January 24, 2006	Receipt of 3rd (Final) FDA revision to labeling text (Label negotiations)
January 24, 2006	Receipt of 2nd FDA revision to packaging (Label negotiations)
January 25, 2006	Submission of 2nd SPI revision to labeling text (Label negotiations)
January 25, 2006	Submission of 2nd SPI revision to packaging (Label negotiations)
January 25, 2006	Response to RFI: Figure 1; revised labeling (Label negotiations)
January 25, 2006	Submission of Other AE listing revision (Proposed revision to labeling)
January 26, 2006	Teleconference with the FDA (Final label negotiations)
January 26, 2006	Receipt of Post-marketing commitments request (Pediatrics; renal; hepatic)
January 26, 2006	Submission of Country of origin on packaging query (Proposed text)
January 26, 2006	Receipt of Other AE listing revision (To be submitted as supplement)
January 27, 2006	Receipt of 3rd (Final) FDA revision to packaging (Agreement letter requested)
January 27, 2006	Submission of Revised Figure 1 of labeling
January 27, 2006	Submission of 3rd (Final) SPI revision to labeling; PMC letter
January 27, 2006	Submission of 3rd (Final) SPI revision to packaging
January 27, 2006	Receipt of Country of origin on packaging
January 28, 2006	3rd (Final) SPI revision to packaging follow-up
January 30, 2006	Submission of post-marketing commitments update
January 31, 2006	Receipt of NDA approval letter (NDA 21-908)
January 31, 2006	NDA approval letter acknowledgement via fax
February 2, 2006	Submission of final labeling and post-marketing commitment letter
February 8, 2006	Authorization for TPNA to submit to DDMAC
February 27, 2006	Submission of patent listing (Orange Book) for Amitiza
March 9, 2006	Submission of IND 59,623 Annual Report

(12) A STATEMENT, BEGINNING ON A NEW PAGE, THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED.

The Applicant is of the opinion that U.S. Patent 5,284,858 is eligible for the extension of patent term applied for under 35 U.S.C. § 156 because it satisfies all the requirements for such extension as follows.

(a) 35 U.S.C. § 156(a)

U.S. Patent 5,284,858 claims a product and a method of using the claimed product that encompass lubiprostone.

(b) 35 U.S.C. § 156(a) (1)

The term of U.S. Patent 5,284,858 expires February 8, 2011 as measured seventeen (17) years from the issue date, and thus, has not expired before submission of this application.

(c) 35 U.S.C. § 156(a) (2)

The term of U.S. Patent 5,284,858 has never been extended.

(d) 35 U.S.C. § 156(a) (3)

The application for extension is submitted by the authorized agent of the owner of record in accordance with the requirements of 35 U.S.C. § 156(d) and the rules of the U.S. Patent and Trademark Office. A copy of a duly executed Power of Attorney and Appointment of Agent is attached hereto as Exhibit 8.

(e) 35 U.S.C. § 156(a) (4)

The product, AMITIZA™ (Lubiprostone) Soft Gelatin Capsules, has been subjected to a regulatory review period as defined in 35 U.S.C. § 156(g) before its commercial marketing or use.

(f) 35 U.S.C. § 156(a) (5) (A)

The commercial marketing or use of the product, AMITIZA™ (Lubiprostone) Soft Gelatin Capsules, after the regulatory review period is the first permitted commercial marketing or use of the product under the provisions of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 355, under which said regulatory review period occurred.

(g) 35 U.S.C. § 156(c) (4)

No other patent has been extended for the same regulatory review period for the product, AMITIZA™ (Lubiprostone) Soft Gelatin Capsules.

(12-A) The length of extension of the patent term of U.S. Patent 5,284,858 claimed by the Applicant is **1251 days**. The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g) (1) (B) began on January 29, 2000, and ended on January 31, 2006, which is a total of 2195 days, which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. § 156(g) (1) (B) (i), the "testing period," began on January 29, 2000 and ended on March 31, 2005, which is 1888 days; and

(ii) The period of review under 35 U.S.C. § 156(g) (1) (B) (ii), the "application period," began on March 31, 2005 and ended on January 31, 2006, which is 307 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph (12-A) (a) above (2195 days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (February 8, 1994) which is zero (0) days, and

(ii) The number of days in which the Applicant did not act with due diligence which is zero (0) days, and

(iii) One-half the number of days determined in subparagraph (12-A) (a) (i) less (b)(i) and (ii) above, or (1888 - 0 - 0) x ½ = 944 days,

which totals 1251 days;

(c) The number of days as determined in subparagraph (12-A) (b) (1251 days) when added to the original term of the patent would result in the date, July 13, 2014;

(d) Fourteen (14) years when added to the date of NDA approval (January 31, 2006), result in the date, January 31, 2020;

(e) The earlier date as determined in subparagraphs (12-A) (c) and (12-A) (d) is July 13, 2014;

(f) The original patent was issued after September 24, 1984. Therefore, five (5) years when added to the original expiration date of the patent (February 8, 2011) would result in the date, February 8, 2016:

(g) The earlier date as determined in subparagraph (12-A) (e) and (12-A) (f) is July 13, 2014.

Therefore, the length of extension of patent term claimed by the Applicant is 1251 days. The date of termination of the extended patent term is not more than 14 years from the date of NDA approval.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT.

The Applicant acknowledges a duty to disclose to the Commissioner of Patent and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION.

The prescribed fee for receiving and acting upon this application is to be charged to the deposit account of the Applicant's agent as authorized in the attached letter, which is submitted in duplicate.

(15) THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED.

All inquires and correspondence should be directed to Bruce E. Kramer and Fang Liu, Ph.D., SUGHRUE MION, PLLC, 2100 Pennsylvania Ave., NW, Suite 800, Washington, D.C. 20037-3213, telephone number (202) 293-7060.

(16) FOUR ADDITIONAL COPIES OF THE APPLICATION PAPERS.

Four duplicates of these Application papers are enclosed as Exhibit 9.

Respectfully submitted,

Bruce E. Kramer
Registration No. 33,725

Fang Liu, Ph.D.
Registration No. 51,283

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: March 27, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 5,284,858

Docket No: Q29894 (ID004406)

Issued: February 8, 1994

Assignee: Sucampo AG

For: PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME

AUTHORIZATION TO CHARGE DEPOSIT ACCOUNT

MAIL STOP: Patent Term Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The USPTO is directed and authorized to charge the statutory fee of $1,120.00, as well as any other required fees, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account. A duplicate copy of this paper is attached.

Respectfully submitted,

Bruce E. Kramer
Registration No. 33,725

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: March 27, 2006

Assignment

SERIAL NO. _____ FILED _____

In consideration of the sum of One Dollar ($1.00) and other good and valuable consideration, the receipt of which is hereby acknowledged,

Insert Name(s) of Inventor(s)

Ryuzo UENO, Ryuji UENO, Ichie Kato and Tomio ODA

(hereinafter designated as the undersigned) hereby sell(s) and assign(s) to

Insert Name of Assignee

KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO

Address of Assignee

of 4-8, 2-chome, Koraibashi, Chuo-ku, Osaka-shi, Osaka-fu, Japan ,

its heirs, successors, legal representatives and assigns (hereinafter designated as the Assignee), the entire right, title and interest in the invention or improvements in

Title of Invention

PROSTAGLANDINS E AND ANTI-ULCERS CONTAINING SAME

for which an application for Letters Patent of the United States of America has been executed by the undersigned

Date of Signing of Application

on September 28, 1989 and September 26, 1989 respectively

The undersigned agree(s) to execute all papers necessary in connection with this application and any continuing, divisional or reissue applications thereof and also to execute separate assignments in connection with such applications as the Assignee may deem necessary or expedient.

The undersigned agree(s) to execute all papers necessary in connection with any interference which may be declared concerning this application or continuation, division or reissue thereof or letters patent or reissue patent issued thereon and to cooperate with the Assignee in every way possible in obtaining and producing evidence and proceeding with such interference.

The undersigned agree(s) to execute all papers and documents and to perform any act which may be necessary in connection with claims or provisions of the International Convention for the Protection of Industrial Property or similar agreements.

The undersigned agree(s) to perform all affirmative acts which may be necessary to obtain a grant of a valid United States patent to the Assignee and to vest all rights therein hereby conveyed to said Assignee as fully and entirely as the same would have been held by the undersigned if this assignment and sale had not been made.

The undersigned hereby authorize(s) and request(s) the Commissioner of Patents to issue any and all Letters Patents of the United States resulting from said application or any division or divisions or continuing or reissue applications thereof to the said Assignee, as Assignee of the entire interest, and hereby covenants that he has (they have) the full right to convey the entire interest herein assigned, and that he has (they have) not executed, and will not execute, any agreement in conflict herewith.

In witness whereof, executed by the undersigned on the date(s) opposite the undersigned name(s).

Date Sep. 28, 1989, Name of Inventor _____ (signature)

Date Sep. 26, 1989, Name of Inventor _____ (signature)

Date Sep. 28, 1989, Name of Inventor _____ (signature)

Date Sep. 28, 1989, Name of Inventor _____ (signature)

Date _____, Name of Inventor _____ (signature)

(This assignment should preferably be acknowledged before a United States Consul or Notary Public. If not, then the execution by the Inventor(s) should be witnessed by at least two other persons who sign here.)

Witness _____

Witness _____

Witness _____

ACKNOWLEDGMENT

_____ }
_____ }

On this _____ day of _____, 19____, before me

personally appeared the above-named _____

_____

_____

to me personally known to be the individual(s) who executed the foregoing assignment, who did acknowledge to me that he (they) executed the same of his (their) own free will for the purposes therein set forth.

Witness my hand and seal the day and year last above given.

RECORDED
PATENT & TRADEMARK OFFICE
OCT 18 89

_____
Official Signature

(SEAL)

_____
Official Title

COMMISSIONER OF PATENTS
AND TRADEMARKS OFFICE

REEL 5167 FRAME 424

ASSIGNMENT

Whereas, Kabushiki Kaisha Ueno Seiyaku Oyo Kenkyujo, a Corporation of Japan, 4-8, Koraibashi, 2-chome, Chuo-ku, Osaka-shi, Osaka-fu, Japan, is the sole owner by Assignment of the following United States Letters Patents and pending application:

U.S. Patent 5,166,174 - Issued November 24, 1992 (USSN 07/700,895)
U.S. Patent 5,225,439 - Issued July 6, 1995 (USSN 07/681,031)
U.S. Patent 5,284,858 - Issued February 8, 1994 (USSN 07/925,220)
U.S. Patent 5,380,709 - Issued January 10, 1995 (USSN 08/053,561)
U.S. Patent 5,428,062 - Issued June 27, 1995 (USSN 08/053,487)
U.S. Patent 5,886,034 - Issued March 23, 1999 (USSN 08/401,675)
U.S. Patent 5,317,032 - Issued May 31, 1994 (USSN 07/996,495)
Pending U.S. Application 09/073,253, filed May 6, 1998

Whereas SUCAMPO AG, a Corporation of Switerzland, having a business address at Graben 5, CH-6300, Zug , Switerzland is desirous of acquiring all rights, title, and interest in and to the aforesaid Letters Patents of the United States, any reissue of any such patent and said pending United States patent application:

Now therefore, for valuable consideration, receipt whereof is hereby acknowledged,

KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO as Assignor, hereby sells, assigns and transfers to the aforesaid SUCAMPO AG, its successors and assigns, the entire right, title and interest in and to the above-named patents, any reissue of any such patent and said pending patent application.

AND said KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO hereby agrees upon request to execute any instrument which SUCAMPO AG desires to carry this Assignment into effect and perfect the title transferred hereby.

IN TESTIMONY WHEREOF the Assignor has executed these presents.

Signed on May 15, 2001

KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO
By: Ryuzo Ueno
Name: Ryuzo UENO
Title: President
KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO

G/ JANNA 8/30 Received

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

AUGUST 25, 2001

PTAS

101753190A

SUGHRUE, MION, ZINN, MACPEAK & SEAS,PLLC
LOUIS GUBINSKY
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, D.C. 20037-3213

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 06/13/2001

REEL/FRAME: 011887/0481
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR''S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO

DOC DATE: 05/15/2001

ASSIGNEE:
SUCAMPO AG
GRABEN 5, CH-6, SWITZERLAND

SERIAL NUMBER: 09073253
PATENT NUMBER: 6265440

FILING DATE: 05/06/1998
ISSUE DATE: 07/24/2001

SERIAL NUMBER: 07700895
PATENT NUMBER: 5166174

FILING DATE: 05/13/1991
ISSUE DATE: 11/24/1992

SERIAL NUMBER: 07681031
PATENT NUMBER: 5225439

FILING DATE: 04/05/1991
ISSUE DATE: 07/06/1993

SERIAL NUMBER: 07925220
PATENT NUMBER: 5284858

FILING DATE: 08/06/1992
ISSUE DATE: 02/08/1994

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of:

Ryuzo UENO, et al. Docket No: 004406

U.S. Patent No.: 5,284,858

Issued: February 8, 1994

For: PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME

LETTER AUTHORIZING RELIANCE ON ACTIVITY BEFORE THE FDA IN ASSOCIATION WITH APPLICATION FOR PATENT TERM EXTENSION

UNDER 35 U.S.C. § 156

MAIL STOP: Patent Term Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

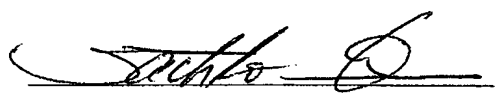
Sucampo Pharmaceuticals, Inc. is the owner of IND 59,623 and NDA 21-908, filed for the approval of the approved product AMITIZA™ (lubiprostone) Soft Gelatin Capsules.

Sucampo Pharmaceuticals, Inc. was the marketing applicant before the FDA during the regulatory review period for IND 59,623 and NDA 21-908. During the regulatory review period for IND 59,623 and NDA 21-908, Sucampo Pharmaceuticals, Inc. had an agency relationship with Sucampo AG of Switzerland.

The undersigned hereby authorizes the applicant for patent term extension, Sucampo AG, to rely on the activities before the FDA pursuant to IND 59,623 and NDA 21-908 in association with the approval of AMITIZA™ (lubiprostone) Soft Gelatin Capsules.

Date: March 10, 2006

Sucampo Pharmaceuticals, Inc.

By: 

Name: Sachiko Kuno, PhD
Title: President and CEO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-908

Sucampo Pharmaceuticals, Inc.
4733 Bethesda Avenue, Suite 450
Bethesda, Maryland 20814

REC'D FEB 03 2006

Dear Dr. Cormack:

Please refer to your new drug application (NDA) dated March 31, 2005, received March 31, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amitiza™ (Lubiprostone Capsules).

We acknowledge receipt of your submissions dated June 9, July 27, September 16, September 30, October 17, November 2, November 16, November 22, December 7, December 9, December 14, December 21, December 23, 2005 and January 3, 2006.

This new drug application provides for the use of Amitiza™ (Lubiprostone Capsules) for the treatment of chronic idiopathic constipation in the adult population.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling and submitted labeling (package insert submitted January 27, 2006 and immediate container and carton labels submitted January 28, 2006). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0 to 17 years until January 31, 2008.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

Deferred pediatric studies under PREA for the treatment of chronic idiopathic constipation in pediatric patients ages 0 to 17 years.

Protocol Submission:	by July 31, 2006
Study Start:	by January 31, 2007
Final Report Submission:	by January 31, 2008

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

We remind you of your postmarketing study commitments in your submission dated January 27, 2006. These commitments are listed below.

1. Perform a Phase IV study to assess the need for potential dose adjustment in patients with renal impairment.

Protocol Submission:	by July 31, 2006
Study Start:	by January 31, 2007
Final Report Submission:	by January 31, 2008

2. Perform a Phase IV study to assess the need for potential dose adjustment in patients with hepatic impairment.

Protocol Submission:	by July 31, 2006
Study Start:	by January 31, 2007
Final Report Submission:	by January 31, 2008

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Tanya Clayton, B.S., Regulatory Health Project Manager at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Acting Director
Office of New Drug Evaluation III
Center for Drug Evaluation and Research

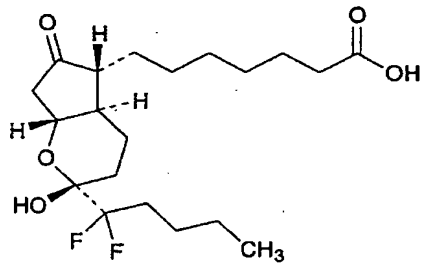
Enclosure

AMITIZA™
(lubiprostone)
Soft Gelatin Capsules

Rx Only, Prescribing Information

DESCRIPTION

AMITIZA™ (lubiprostone) is chemically designated as (–)-7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid. The molecular formula of lubiprostone is $C_{20}H_{32}F_2O_5$ with a molecular weight of 390.46 and a chemical structure as follows:



Lubiprostone drug substance occurs as white, odorless crystals or crystalline powder and is very soluble in ether and ethanol, and practically insoluble in hexane and water. AMITIZA™ is available for oral administration in an imprinted, oval, orange, soft gelatin capsule containing 24 mcg lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, FD&C Red #40, D&C Yellow #10, and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Chronic idiopathic constipation is generally defined by infrequent or difficult passage of stool. The signs and symptoms associated with chronic idiopathic constipation (*i.e.*, abdominal pain or discomfort, bloating, straining, and hard or lumpy stools) may be the result of abnormal colonic motility that can delay the transit of intestinal contents and impede the evacuation of rectal contents. One approach to the treatment of chronic idiopathic constipation is the secretion of fluid into the

abdominal lumen through the activation of chloride channels in the apical membrane of the gastrointestinal epithelium.

Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating ClC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A–independent fashion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. Patch clamp cell studies in human cell lines have indicated that the majority of the beneficial biological activity of lubiprostone and its metabolites is observed only on the apical (luminal) portion of the gastrointestinal epithelium.

Pharmacokinetics:

Lubiprostone has low systemic availability following oral administration and concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/mL). Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), C_{max}, and $t_{½}$ cannot be reliably calculated. However, the pharmacokinetic parameters of M3 (only measurable active metabolite) have been characterized.

Absorption:

Concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/mL) because lubiprostone has a low systemic availability following oral administration. Peak plasma levels of M3, after a single oral dose of 24 mcg of lubiprostone, occur at approximately 1.14 hours. The C_{max} was 41.9 pg/mL and the mean AUC was 59.1 pg•hr/mL. AUC of M3 increases dose proportionally after single 24-mcg and 144-mcg doses of lubiprostone.

Distribution:

In vitro protein binding studies indicate lubiprostone is approximately 94% bound to human plasma proteins. Studies in rats with radiolabeled lubiprostone indicate minimal distribution beyond the gastrointestinal tissues. Concentrations of radiolabeled compound at 48 hours post-administration were minimal in all tissues.

Metabolism:

The results of both human and animal studies indicate that lubiprostone is rapidly and extensively metabolized by 15-position reduction, α-chain β-oxidation, and ω-chain ω-oxidation. These biotransformations are not mediated by the hepatic cytochrome P450 system but rather appear to be mediated by the ubiquitously expressed carbonyl reductase. M3, a metabolite of lubiprostone in both humans and animals is formed by the reduction of the carbonyl group at the 15-hydroxy moiety that consists of both α-hydroxy and β-hydroxy epimers. M3 makes up less than 10% of the dose of radiolabeled lubiprostone. Animal studies have shown that metabolism of lubiprostone rapidly occurs within the stomach and jejunum, most likely in the absence of any systemic absorption. This is presumed to be the case in humans as well.

Elimination:

Lubiprostone could not be detected in plasma; however, M3 has a $t_{½}$ ranging from 0.9 to 1.4 hours. After a single oral dose of 72 mcg of ^{3}H-labeled lubiprostone, 60% of total administered radioactivity was recovered in the urine within 24 hours and 30% of total administered radioactivity was recovered in the feces by 168 hours. Lubiprostone and M3 are only detected in trace amounts in feces in humans.

Food Effect:

A study was conducted with a single 72-mcg dose of ^{3}H-labeled lubiprostone to evaluate the potential of a food effect on lubiprostone absorption, metabolism, and excretion (AME). Pharmacokinetic parameters of total radioactivity demonstrated that C_{max} decreased by 55% while $AUC_{0-\infty}$ was unchanged when lubiprostone was administered with a high-fat meal. The clinical relevance of the effect of food on the pharmacokinetics of lubiprostone is not clear. However, lubiprostone was administered with food in a majority of clinical trials.

Special Populations:

Gender:

Gender has no effect on the pharmacokinetics of M3 when lubiprostone is dosed.

Hepatic Impairment:

Lubiprostone has not been studied in hepatically impaired populations.

Renal Impairment:

Lubiprostone has not been studied in renally impaired populations.

CLINICAL STUDIES

A dose-finding, double-blind, parallel-group, placebo-controlled, Phase 2 study was conducted in patients with chronic idiopathic constipation. Following a 2-week baseline/washout period, patients received 3 weeks of double-blind medication. Patients (n = 127) were randomized to receive placebo (n = 33), AMITIZA™ 24 mcg/day (24 mcg QD; n = 29), AMITIZA™ 48 mcg/day (24 mcg BID; n = 32), or AMITIZA™ 72 mcg/day (24 mcg TID; n = 33). Patients were chosen for participation based on their need for relief of constipation, which was defined as < 3 spontaneous bowel movements (SBMs) per week. The primary efficacy variable was the daily average number of SBMs.

The study demonstrated that all patients who took AMITIZA™ experienced a noticeable improvement in clinical response. Based on the efficacy analysis, there was no statistically significant improvement in the clinical response beyond a total daily dose of 24 mcg between treatment weeks 2 and 3 (Figure 1).

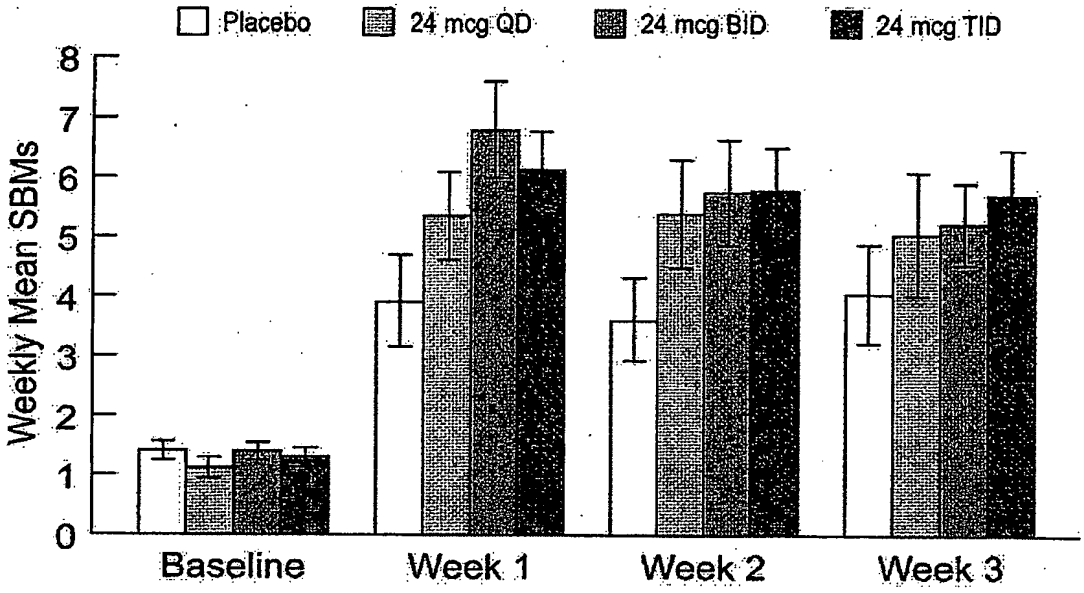


Figure 1: Weekly Mean (± Standard Error) Spontaneous Bowel Movements (Dose-finding Study)

Two double-blind, placebo-controlled studies of identical design were conducted in patients with chronic idiopathic constipation. Chronic idiopathic constipation was defined as, on average, less than 3 SBMs per week with one or more of the following symptoms for constipation for at least 6 months prior to randomization: 1) very hard stools for at least a quarter of all bowel movements; 2) sensation of incomplete evacuation following at least a quarter of all bowel movements; and 3) straining with defecation at least a quarter of the time.

Following a 2-week baseline/washout period, a total of 479 patients (88.9% female, mean age 47.2 [range 20.0–81.0], 80.8% Caucasian, 9.6% African American, 10.9% ≥ 65 years of age) were randomized to receive 4 weeks of double-blind treatment with either AMITIZA™ 24 mcg BID (48 mcg/day) or placebo. The primary endpoint of the studies was SBM frequency following initiation of double-blind treatment. The studies demonstrated that patients treated with AMITIZA™ had a higher frequency of SBMs during Week 1 than the placebo patients. In both studies, results similar to those in Week 1 were also observed in Weeks 2, 3, and 4 of therapy.

Table 1: Spontaneous Bowel Movement Frequency Rates – AMITIZA™ 24 mcg BID vs. Placebo

Trial	Study Arm	Baseline *Mean ± SD Median*	Week 1 *Mean ± SD Median*	Week 2 *Mean ± SD Median*	Week 3 *Mean ± SD Median*	Week 4 *Mean ± SD Median*	Week 1 Change from Baseline *Mean ± SD Median*	Week 4 Change from Baseline *Mean ± SD Median*
Study 1	Placebo	1.6 ± 1.3 1.5	3.5 ± 2.3 3.0	3.2 ± 2.5 3.0	2.8 ± 2.2 2.0	2.9 ± 2.4 2.3	1.9 ± 2.2 1.5	1.3 ± 2.5 1.0
	AMITIZA™	1.4 ± 0.8 1.5	5.7 ± 4.4 5.0	5.1 ± 4.1 4.0	5.3 ± 4.9 5.0	5.3 ± 4.7 4.0	4.3 ± 4.3 3.5	3.9 ± 4.6 3.0
Study 2	Placebo	1.5 ± 0.8 1.5	4.0 ± 2.7 3.5	3.6 ± 2.7 3.0	3.4 ± 2.8 3.0	3.5 ± 2.9 3.0	2.5 ± 2.6 1.5	1.9 ± 2.7 1.5
	AMITIZA™	1.3 ± 0.9 1.5	5.9 ± 4.0 5.0	5.0 ± 4.2 4.0	5.6 ± 4.6 5.0	5.4 ± 4.8 4.3	4.6 ± 4.1 3.8	4.1 ± 4.8 3.0

The above frequency rates are calculated as 7 times (number of SBMs) / (number of days observed for that week).

In both studies, AMITIZA™ demonstrated increases in the percentage of patients who experienced SBMs within the first 24 hours after administration when compared to placebo (56.7% vs. 36.9% in Study 1 and 62.9% vs. 31.9% in Study 2, respectively). Similarly, the time to first SBM was shorter for AMITIZA™ patients than for those receiving placebo.

Signs and symptoms related to constipation, including abdominal bloating, abdominal discomfort, stool consistency, and straining, as well as constipation severity ratings, were also improved in AMITIZA™ patients versus placebo. The results were consistent in subpopulation analysis for gender, race, and elderly patients (≥ 65 years of age).

Following 4 weeks of treatment with AMITIZA™ 24 mcg BID, withdrawal of AMITIZA™ did not result in a rebound effect.

Long-term Clinical Studies:

Three open-label, long-term clinical safety studies were conducted in patients with chronic idiopathic constipation receiving 24 mcg BID. These studies included 871 patients (86.1% female, mean age 51 [range 19–86] years, 87% Caucasian, 7.3% African American, 18.4% ≥ 65 years of age) who were treated for 6–12 months (24–48 weeks). Patients provided regular assessments of abdominal bloating, abdominal discomfort, and constipation severity. The results of these studies demonstrated that AMITIZA™ decreased abdominal bloating, abdominal discomfort, and constipation severity over the 6–12 month treatment periods.

INDICATION AND USAGE

AMITIZA™ is indicated for the treatment of chronic idiopathic constipation in the adult population.

CONTRAINDICATION

AMITIZA™ is contraindicated in those patients with a known hypersensitivity to the drug or any of its excipients, and in patients with a history of mechanical gastrointestinal obstruction.

WARNING

Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be evaluated prior to initiating AMITIZA™ treatment.

The safety of AMITIZA™ in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to have the potential to cause fetal loss. AMITIZA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with AMITIZA™ and should be capable of complying with effective contraceptive measures (see TERATOGENIC EFFECTS: PREGNANCY CATEGORY C).

PRECAUTIONS

Patient Information:

AMITIZA™ may cause nausea. If this occurs, concomitant administration of food with AMITIZA™ may reduce symptoms of nausea. AMITIZA™ should not be administered to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. If the diarrhea becomes severe consult your physician.

Drug Interactions:

Based upon the results of *in vitro* human microsome studies, there is low likelihood of drug–drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to M3. Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit

cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies in primary cultures of human hepatocytes show no induction of the cytochrome P450 isoforms 1A2, 2B6, 2C9 and 3A4. No additional drug–drug interaction studies have been performed. Based on the available information, no protein binding–mediated drug interactions of clinical significance are anticipated.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis:

Two 2-year oral (gavage) carcinogenicity studies (one in Crl:B6C3F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the 2-year carcinogenicity study in mice, lubiprostone doses of 25, 75, 200, and 500 mcg/kg/day (approximately 2, 6, 17, and 42 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, lubiprostone doses of 20, 100, and 400 mcg/kg/day (approximately 3, 17, and 68 times the recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidences. There was a significant increase in the incidence of interstitial cell adenoma of the testes in male rats at the 400 mcg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 mcg/kg/day dose.

Lubiprostone was not genotoxic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma (L5178Y TK+/–) forward mutation assay, the *in vitro* Chinese hamster lung (CHL/IU) chromosomal aberration assay, and the *in vivo* mouse bone marrow micronucleus assay.

Lubiprostone, at oral doses of up to 1000 mcg/kg/day, had no effect on the fertility and reproductive function of male and female rats. The 1000 mcg/kg/day dose in rats is approximately 166 times the recommended human dose of 48 mcg/day, based on the body surface area.

TERATOGENIC EFFECTS: PREGNANCY CATEGORY C

Teratology studies with lubiprostone have been conducted in rats at oral doses up to 2000 mcg/kg/day (approximately 332 times the recommended human dose, based on body surface area), and in rabbits at oral doses of up to 100 mcg/kg/day (approximately 33 times the recommended human dose, based on body surface area). Lubiprostone was not teratogenic in rats and rabbits. In guinea pigs, lubiprostone

caused fetal loss at repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the human dose, respectively, based on body surface area) administered on days 40 to 53 of gestation.

There are no adequate and well-controlled studies in pregnant women. However, during clinical testing of AMITIZA™ at 24 mcg BID, four women became pregnant. Per protocol, AMITIZA™ was discontinued upon pregnancy detection. Three of the four women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the patient was subsequently lost to follow-up.

AMITIZA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman is or becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers:
It is not known whether lubiprostone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lubiprostone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
AMITIZA™ has not been studied in pediatric patients.

Renal Impaired:
AMITIZA™ has not been studied in patients who have renal impairment.

Hepatic Impaired:
AMITIZA™ has not been studied in patients who have hepatic impairment.

ADVERSE REACTIONS
In clinical trials, 1429 patients received AMITIZA™ 24 mcg BID or placebo. Table 2 presents data for the adverse experiences that were reported in at least 1% of patients who received AMITIZA™ and that occurred more frequently on study drug than placebo. It should be noted that the placebo data presented are from short-term exposure (≤4 weeks) whereas the AMITIZA™ data are cumulative data

that were collected over 3- or 4-week, 6-month and 12-month observational periods and that some conditions are common among otherwise healthy patients over a 6- and 12-month observational period.

Table 2: Adverse Events Reported for Patients Treated with AMITIZA™

System/Adverse Experience	Placebo n = 316 %	AMITIZA™ 24 mcg QD n = 29 %	AMITIZA™ 24 mcg BID n = 1113 %	AMITIZA™ Any Active Dose[1] n = 1175 %
Gastrointestinal disorders				
Nausea	5.1	17.2	31.1	30.9
Diarrhea	0.9	10.3	13.2	13.2
Abdominal distension	2.2	0.0	7.1	6.8
Abdominal pain	2.8	3.4	6.7	6.8
Flatulence	1.9	3.4	6.1	5.9
Vomiting	0.9	0.0	4.6	4.4
Loose stools	0.0	0.0	3.4	3.2
Dyspepsia	1.3	0.0	2.9	2.7
Abdominal pain upper	1.9	0.0	2.2	2.1
Abdominal pain lower	0.6	0.0	1.9	1.8
Gastroesophageal reflux disease	0.6	0.0	1.8	1.7
Abdominal discomfort	0.0	3.4	1.5	1.5
Dry mouth	0.3	0.0	1.5	1.4
Constipation	0.9	0.0	1.1	1.0
Stomach discomfort	0.3	0.0	1.1	1.0
Infections and Infestations				
Sinusitis	1.6	0.0	4.9	4.8
Urinary tract infections	1.9	3.4	4.4	4.3
Upper respiratory tract infection	0.9	0.0	3.7	3.6
Nasopharyngitis	2.2	0.0	2.9	2.7
Influenza	0.6	0.0	2.0	1.9
Bronchitis	0.3	3.4	1.6	1.7
Gastroenteritis viral	0.0	3.4	1.0	1.0
Viral infection	0.3	3.4	0.5	0.6
Nervous system disorders				
Headache	6.6	3.4	13.2	13.0
Dizziness	1.3	3.4	4.1	4.0
Hypoesthesia	0.0	3.4	0.5	0.6
General disorders and site administration conditions				
Edema peripheral	0.3	0.0	3.8	3.6
Fatigue	1.9	6.9	2.3	2.5
Chest discomfort	0.0	3.4	1.6	1.6
Chest pain	0.0	0.0	1.1	1.0
Pyrexia	0.3	0.0	1.1	1.0
Musculoskeletal and connective tissue disorders				
Arthralgia	0.3	0.0	3.1	3.0
Back pain	0.9	3.4	2.3	2.3
Pain in extremity	0.0	3.4	1.9	1.9
Muscle cramp	0.0	0.0	1.0	0.9
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	0.0	3.4	2.4	2.5
Pharyngolaryngeal pain	2.2	0.0	1.7	1.6
Cough	0.6	0.0	1.6	1.5
Investigations				
Weight increased	0.0	0.0	1.0	0.9
Psychiatric disorders				
Depression	0.0	0.0	1.4	1.4
Anxiety	0.3	0.0	1.4	1.4
Insomnia	0.6	0.0	1.4	1.4

Vascular disorders				
Hypertension	0.0	0.0	1.0	0.9

[1]Includes patients dosed at 24 mcg QD, 24 mcg BID, and 24 mcg TID

AMITIZA ™-induced Nausea:

Among constipated patients, 31.1% of those receiving AMITIZA™ 24 mcg BID reported nausea. Of those patients, 3.4% reported severe nausea and 8.7% discontinued treatment due to nausea. It should be noted that the incidence of nausea increased in a dose-dependent manner with the lowest overall incidence for nausea seen at the 24 mcg QD dose (17.2%). Further analysis of nausea has shown that long-term exposure to AMITIZA™ does not appear to place patients at elevated risk for experiencing nausea. In the open-label, long-term studies, patients were allowed to titrate the dose of AMITIZA™ down to 24 mcg QD from 24 mcg BID if experiencing nausea. It should also be noted that nausea decreased when AMITIZA™ was administered with food and that, across all dose groups, the rate of nausea was substantially lower among constipated men (13.2%) and constipated elderly patients (18.6%) when compared to the overall rate (30.9%). No patients in the trials were hospitalized due to nausea.

AMITIZA ™-induced Diarrhea:

Among constipated patients, 13.2% of those receiving AMITIZA™ 24 mcg BID reported diarrhea. Of those patients, 3.4% reported severe diarrhea and 2.2% discontinued treatment due to diarrhea. The incidence of diarrhea did not appear to be dose-dependent. No serious adverse events were reported for electrolyte imbalance in the six clinical trials and no clinically significant changes were seen in serum electrolyte levels while patients were receiving AMITIZA™.

Other Adverse Events:

The following list of adverse events include those that were considered by the investigator to be possibly related to AMITIZA™ and reported more frequently (>0.2%) on AMITIZA™ than placebo and those that lead to discontinuation more frequently (≥0.2%) on AMITIZA™ than placebo. Although the events reported occurred during treatment with AMITIZA™, they were not necessarily attributed to dosing of AMITIZA™:

- **Gastrointestinal disorders:** watery stools, fecal incontinence, abnormal bowel sounds, frequent bowel movements, retching

- **Nervous system disorders:** syncope, tremor, dysgeusia, paraesthesia
- **General disorders and administration site conditions:** rigors, pain, asthenia, malaise, edema
- **Respiratory, thoracic, and mediastinal disorders:** asthma, painful respiration, throat tightness
- **Skin and subcutaneous tissue disorders:** hyperhidrosis, urticaria, rash
- **Psychiatric disorders:** nervousness
- **Vascular disorders:** flushing, palpitations
- **Metabolism and nutrition disorders:** decreased appetite
- **Ear and labyrinth disorders:** vertigo

Overdosage:

There have been two confirmed reports of overdosage with AMITIZA™. The first report involved a 3-year-old child who accidentally ingested 7 to 8 capsules of 24 mcg of AMITIZA™ and fully recovered. The second report was a study subject who self-administered a total of 96 mcg AMITIZA™ per day for 8 days. The subject experienced no adverse events during this time. Additionally, in a definitive Phase 1 cardiac repolarization study, 51 patients administered a single oral dose of 144 mcg of AMITIZA™, which is 6 times the normal single administration dose. Thirty-nine (39) of the 51 patients experienced an adverse event. The adverse events reported in >1% of this group included the following: nausea (45.1%), vomiting (27.5%), diarrhea (25.5%), dizziness (17.6%), loose or watery stools (13.7%), headache (11.8%), retching (7.8%), abdominal pain (5.9%), flushing or hot flush (5.9%), dyspnea (3.9%), pallor (3.9%), stomach discomfort (3.9%), syncope (3.9%), upper abdominal pain (2.0%), anorexia (2.0%), asthenia (2.0%), chest discomfort (2.0%), dry mouth (2.0%), hyperhidrosis (2.0%), skin irritation (2.0%) and vasovagal episode (2.0%).

DOSAGE AND ADMINISTRATION

The recommended dosage for AMITIZA™ is 24 mcg taken twice daily (BID) orally with food. Physicians and patients should periodically assess the need for continued therapy.

HOW SUPPLIED

AMITIZA™ is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 mcg lubiprostone. AMITIZA™ is available as follows:

Bottles of 100.....NDC 64764-240-10

STORAGE

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

MARKETED BY:

Sucampo Pharmaceuticals, Inc.
Bethesda, MD 20814

and

Takeda Pharmaceuticals America, Inc.
Lincolnshire, IL 60069

PRODUCT OF THE UNITED STATES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

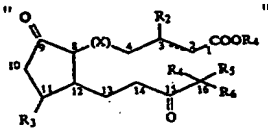
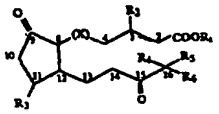
Julie Beitz
1/31/2006 10:10:02 AM

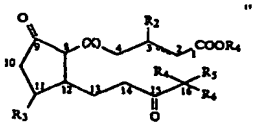
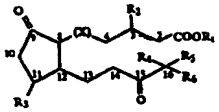
UNITED STATES PATENT AND TRADEMARK OFFICE

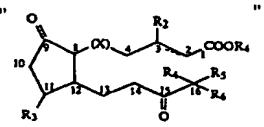
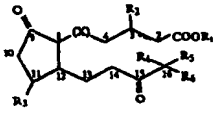
CERTIFICATE OF CORRECTION

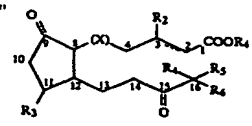
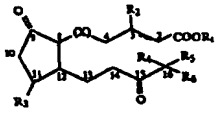
PATENT NO. : 5,284,858
DATED : February 8, 1994
INVENTOR(S) : Ryuzo Ueno et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 3,
Line 1, delete "  " and insert --  --.

Column 77,
Line 50, delete "  " and insert --  --.

Column 78,
Line 30, delete "  " and insert --  --.

Column 79,
Line 11, delete "  " and insert --  --.

Signed and Sealed this

Seventh Day of September, 2004

JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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COMPUTER PACKAGES, INC.
414 HUNGERFORD DRIVE
ROCKVILLE MD 20850

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,284,858	**$1,020.00**	**$0.00**	**07/925,220**	**02/08/94**	**08/06/92**	**04**	**NO**	**PAID**	**Q-29894**

Direct any questions about this notice to:
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5,284,858	**$1,950.00**	**$0.00**	**07/925,220**	**02/08/94**	**08/06/92**	**08**	**NO**	**PAID**	**Q-29894**

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,284,858	**$3,800.00**	**$0.00**	**07/925,220**	**02/08/94**	**08/06/92**	**12**	**NO**	**PAID**	**Q-29894**

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OIPE IAP13 MAR 27 2006 PATENT & TRADEMARK OFFICE

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 08/31/06
See OMB Statement on Page 3.

NDA NUMBER
21908

NAME OF APPLICANT / NDA HOLDER
Sachiko Kuno, PhD
CEO, Sucampo Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ETREVA

ACTIVE INGREDIENT(S)	STRENGTH(S)
Lubiprostone	24 mcg

DOSAGE FORM
Liquid Gelatin Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5284858	2/8/1994	2/8/2011

d. Name of Patent Owner
Sucampo AG

Address *(of Patent Owner)*
Graben 5,

City/State
Zug, Switzerland

ZIP Code	FAX Number *(if available)*
CH-6300	41-1-252-9804
Telephone Number	**E-Mail Address *(if available)***
41-1-262-4678	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*
4733 Bethesda Ave, Ste 450

City/State
Bethesda, MD

ZIP Code	FAX Number *(if available)*
20814	301.961.3440
Telephone Number	**E-Mail Address *(if available)***
301.961.3400	s kuno@sucampo.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	03/21/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Sachiko Kuno, PhD, CEO, Sucampo Pharmaceuticals, Inc.	
Address 4733 Bethesda Ave, Ste 450	City/State Bethesda, MD
ZIP Code 20814	Telephone Number 301.961.3400
FAX Number *(if available)* 301.961.3440	E-Mail Address *(if available)* s.kuno@sucampo.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of:

Ryuzo UENO, et al. Docket No: 004406

U.S. Patent No.: 5,284,858

Issued: February 8, 1994

For: PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME

POWER OF ATTORNEY AND APPOINTMENT OF AGENT

PURSUANT TO 37 C.F.R. § 1.730

MAIL STOP: Patent Term Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant, Sucampo AG, a corporation organized and existing under the laws of Switzerland, and having a principal place of business at Graben 5, CH-6300, Zug, Switzerland, represents that it is the Assignee of the entire right, title and interest in and to United States Letters Patent No. 5,284,858, granted to Ryuzo Ueno, Ryuji Ueno, Ichie Kato and Tomio Oda on February 8, 1994, for PROSTAGLANDINS E AND ANTI ULCERS CONTAINING SAME by virtue of an Assignment from the inventors in favor of Kabushiki Kaisha Ueno Seiyaku Oyo Kenkyujo, recorded in the U.S. Patent and Trademark Office on October 18, 1989, at Reel 5167, Frame 423-424, and subsequently, an Assignment from Kabushiki Kaisha Ueno Seiyaku Oyo Kenkyujo to Sucampo AG, recorded in the U.S. Patent and Trademark Office on June 13, 2001, at Reel 011887, Frame 0481.

POWER OF ATTORNEY AND APPOINTMENT OF AGENT PURSUANT TO 37 C.F.R. § 1.730
U.S. Patent No.: 5,284,858

Attorney Docket No. 004406

Applicant, Sucampo AG, as the owner of record of the above-identified United States Letters Patent, hereby appoints the practitioners at CUSTOMER NO. 23373 (SUGHRUE MION, PLLC) as its attorneys to conduct all business before the United States Patent and Trademark Office relative to an application for patent term extension pursuant to 35 U.S.C. § 156 for the above-identified United States Letters Patent.

It is requested that all correspondence relative to the same be directed to Bruce E. Kramer, SUGHRUE MION, PLLC, 2100 Pennsylvania Ave., N.W., Washington, DC 20037-3213, whose telephone number is (202) 293-7060, and any telephonic communications relative to the same are also to be conducted with one of the attorneys listed under CUSTOMER NO. 23373 at the telephone number listed immediately above.

The undersigned (whose title is supplied below) is empowered to sign this Power of Attorney and Appointment of Agent on behalf of the Assignee.

Date: March 22, 2006

Sucampo AG

By: Misako Nakata

Name: Misako Nakata
Title: Authorized Signing Officer

EXHIBIT 1